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Prevalence and incidence of dementia and interaction between genetic admixture, apoe genotype, lipids and dementia in an admixed Cuban population

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Author:Juan Llibre Rodriguez

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**PREVALENCE AND INCIDENCE OF DEMENTIA AND
INTERACTION BETWEEN GENETIC ADMIXTURE, APOE
GENOTYPE, LIPIDS AND DEMENTIA IN AN ADMIXED CUBAN
POPULATION**

Juan de Jesús Llibre Rodríguez

**Thesis submitted for the degree of Doctor of Philosophy to the
University of London**

December, 2011

Institute of Psychiatry, King's College London, University of London

Statement of candidate's contribution to the work

The research carried out in this thesis was part of a larger study funded by the Wellcome Trust Foundation in which I have been involved for almost ten years in one of the 10/66 centres as a principal investigator. I have conducted the 10/66 pilot and cross sectional studies in Cuba as principal investigator and I have a role in coordinating, doing quality controls as well as conducting some interviews myself. These gave me a complete understanding of the design, measurements and procedures used in the studies, and a familiarity with all the variables I had used in the analysis for my PhD.

Although I have worked only in one 10/66 centre (Cuba), I have been in direct and constant contact with the other centres, sharing experiences and difficulties that arise from the data collection. I have spent 12 months in London, where I have been taken statistical courses and conducted the analysis under supervision of my supervisors, Dr Ferri and Prof. Prince.

I participated in the design of the study and in the development of the funding proposal with my supervisors. Regarding quality control, I co-ordinated the field work and worked closely with the research team. I supervised personally 5 % of all interviews, participated in the translation process and took the lead on analysis and interpretation. For the reliability and validation studies, I was closely involved in training data collectors, and coordinated the studies, double-entered the data and independently conducted the analyses. I worked closely with my supervisors to design the study

questionnaire and train data collectors. For the quantitative analyses presented in this thesis, I developed the analysis plan, conducted the analyses and I am responsible for the interpretation of the findings. I also completed the literature review to include existing research into demographic ageing, epidemiological transition, dementia, and other non communicable diseases among older people and also to review the literature related to the origin of admixture in Cuba and the use of population admixture to understand the aetiology of chronic conditions.

The initial plan for my thesis was to have modelled dementia prevalence, using mixed effects multi-level models across the ten urban and rural sites in the seven LMIC included in the 10/66 Dementia Research program. As part of the initial stages of this work, I took a role in the drafting of a paper published in the Lancet in 2008 (Annex 1) on the prevalence of dementia in Latin America, India and China. However, initial analyses indicated problems with the original plan - the mixed effects models would not converge even when one or two effects were considered at the site-level, presumably because of insufficient variance at site level. I therefore changed my plans for my thesis, to study in detail the epidemiology of dementia (prevalence, incidence and aetiology) specifically in the Cuban population, of particular interest given the island's history, and the high level of ancestry admixture. In the course of my work on the revised plans for the thesis, I have published two further related papers as first author, one on the prevalence, correlates and impact of dementia in Cuba published in Neuroepidemiology in 2008 (Annex 2) and another on the interaction between genetic admixture, ethnic identity, APOE genotype and dementia, published in the BMC Medical Genetics in 2011 (Annex 3).

Abstract

Background: There is a high frequency of the risk-conferring APOE e4 allele in African populations, but in some studies, the risk of dementia is less than in Caucasians in Europe and North America. In an admixed population of older Cubans I estimate the prevalence, incidence, correlates and impact of dementia among older Cubans; I assess the effects of reported ethnicity, admixture and apolipoprotein E genotype on dementia prevalence and estimate the association between cardiovascular risk factors and dementia incidence.

Methods: I undertook a one phase survey (baseline) of all over 65 year old residents of seven catchment areas in Cuba (n=2944) during 2003 to 2007. Dementia diagnosis was established according to DSM-IV and 10/66 criteria. APOE genotype was determined in 2520 participants, and genetic admixture in 235 dementia cases and 349 controls. Baseline data was used to estimate prevalence, impact, and the effect of ethnicity, and apolipoprotein E genotype on dementia prevalence. The case control study was used to test the hypothesis that the effect of APOE genotype on dementia is modified by ethnic group. An incidence wave was conducted 4.5 years after cohort inception in order to estimate incidence and cardiovascular risk factors associations

Results: The prevalence of DSM-IV dementia was 6.4% and 10.8% according to the 10/66. Both dementia outcomes were associated with older age, less education, a family history of dementia, shorter leg length and smaller skull circumference. Dementia, rather than physical health problems or depression, was the main contributor to needs for care and caregiver cutting back on work. The incidence rate of 10/66 dementia was 20.5 per 1000/pyear (95% CI, 17.6-23.5). African admixture was linearly related to number of

APOE e4 alleles, but was not associated with the prevalence of dementia. However, when the effects of 'black' ethnicity and African admixture were considered simultaneously the former was inversely and the latter positively associated with dementia risk. APOE genotype was associated cross-sectionally with dementia prevalence, but the effect on the incidence of dementia was much attenuated, and only apparent among those in the youngest age group. There were no associations between hypertension, diabetes, lipid profile, smoking and the incidence of dementia. There was only weak evidence to support effect modification by APOE genotype.

Conclusion: The prevalence and incidence of dementia in the older cuban population studied is high, and the rate increases with age. These findings underscore the need to improve our understanding of risk factors associated with dementia in specific populations, as well as the need for public health programs for both patients and caregivers in a population that is currently undergoing rapid demographic ageing and epidemiological transition. Counter to our hypothesis, African admixture may be associated with higher risk of dementia.

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I am very grateful to my supervisor, Dr. Cleusa Ferri, for her guidance, comments and support to throughout the whole stage of my project.

I also thank Prof. Martin Prince, for his constructive feedback and recommendation that made this work possible.

Both had changed my vision of the Medicine, previously adressed to the diagnosis and treatment of individual patients, towards to a global vision of the public health.

I would like to thank the members of my research team and all the colleagues of the 10/66 Dementia Research Group around the world.

I would like to express my sincere gratitude to the elderly people who participated in the study. The co-operation of the patients and theirs families have contributed to a better understanding of dementia and other non-communicable diseases, in our country.

Finally, to my wife, Milagros and sons, Juan Carlos and Jorge, without their support and understanding, I could not have finished this arduous work.

Dedicated to

My parents

&

My beloved wife, Milagros

My wonderful sons Juan Carlos and Jorge

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CHAPTER 1 BACKGROUND

1.1 Ageing Populations

1.1.1 Demographic Ageing

The past fifty years have seen increasingly rapid advances in human development. One of the most important achievements is demographic ageing, which is happening rapidly in all world regions, particularly in low and middle income countries. The total global population is projected to rise to 9.2 billion in 2050 representing an increase of 2.7 billion over the 2005 population of 6.5 billion. Nearly all of this future growth will occur in the ‘South’—i.e. Africa, Asia (excluding Japan, Australia and New Zealand), and Latin America where population size is projected to increase from 5.3 to 7.9 billion between 2005 and 2050 (United Nations, 2002, Bongaarts, 2009).

This change will lead to a dramatic increase in the number and proportion of older persons. The global number of people aged 60 years or over will nearly triple, increasing from 606 million in 2000 to nearly 1.9 billion by 2050 (Bongaarts, 2009) . The rise in the proportion of the population aged 60 or over will increase from 19% to 32% in developed regions and from 8% to 20% in less developed regions by 2050 (Christensen et al., 2009, Bongaarts, 2009).

Even more striking is the expected increase in the number of the oldest-old (80 years or over) at the global level from 69 million in 2000 to 377 million in 2050. These rapid changes will affect dramatically the demographic balance between and within geographic regions. In less developed regions the increase will be from 32 million to 265 million, in other words the majority of the oldest old will be living in less developed countries by 2050 (World Health Organisation, 2008b, World Health Organisation, 2008a).

1.1.2 Ageing in Latin America and the Caribbean

Latin America and the Caribbean countries are experiencing unprecedentedly rapid demographic ageing. By 2030 the numbers of people aged 60 years or over will be three times the numbers in 2000. The length of time taken for the proportion of those aged 60 year and over to increase from 8% to 15% in the Latin American and Caribbean corresponds to less than two-fifths the length of time it took in the United States, and between one-fifths and two-fifths of the time it took in an average Western European country to reach similar levels (Palloni et al., 2002).

The most important contributors to this demographic ageing are changes in both fertility and mortality risk from age 0 to 60, which was experienced by many countries in this region after 1940. Argentina and Uruguay exhibited relative low fertility rates before the 50's, while Chile, Cuba and Costa Rica exhibited a rapid fertility rate decline after 1950.

In the remaining countries in this area this happened only after 1975 (Demographic Bulletin Economic Commission for Latin American and the Caribbean, 2003; Palloni et al., 2002).

In the last half century the average life expectancy at birth in the region increased by approximately 20 years, from 50 to 70, and the overall fertility rate decreased by half, from approximately six children to fewer than three (Demographic Bulletin Economic Commission for Latin American and the Caribbean, 2003). Over the same period, the proportion of persons aged 60 years and over rose from 6% to 8%. In 2000-2025 people aged 60 years and over will grow three times faster than the population as a whole and five times faster over the period 2025-2050. As a result, by 2050, one out of every four Latin Americans will be an older adult (United Nations, 2004) .

1.1.3 The health transition

As populations age, non-communicable diseases (NCDs) assume a progressively greater significance in low and middle income countries (LMIC). This process, referred to as the health transition or epidemiologic transition, can be defined as the complex changes in patterns of health, disease, and mortality that result from demographic and associated economic and societal changes in a world population in which infectious diseases are gradually replaced by chronic, degenerative diseases as the leading causes of death (Omran, 1971, Salomon J, 2002) .

Over the next decade deaths from infectious diseases, maternal and perinatal conditions, and nutritional deficiencies combined are projected to decline by 3% worldwide. However, deaths due to chronic diseases are projected to increase by 17% over the same period. Of the projected 64 million people who will die in 2015, 41 million (64 %) will die of a chronic disease (Lopez A.D, 2006).

Latin America exemplifies the third stage of health transition. The region has experienced important changes in health conditions related to demographic structure, improvements in medical care and changing socioeconomic and environmental conditions, as a result of industrialisation and urbanisation. However, paradoxically the increase of about 20 years in life expectancy comes together with adverse changes in life style and cardiovascular risk factor profile, including high fat diets, cigarette smoking and lack of exercise. For this reason CVDs are considered to have maximum public health salience in the Latin American region - more so than in stage 2 regions (China and India) where risk exposure levels are not yet so high. In regions in stage 4, such as Western Europe, North America (excluding some parts of Mexico), Australia, and New Zealand public health measures have led to reduced exposure levels, hence preventing or delaying these diseases to more advanced ages (Yusuf et al., 2001a). INTERHEART, a multinational, case-control study, demonstrate that risk factors for myocardial infarction operate similarly in both sexes and at all ages in all regions of the world, including Latin America and China (Yusuf et al., 2004).

NCDs account for 44% of premature deaths and are already the leading causes of death in all world regions apart from sub-Saharan Africa. As an illustration, the number of

deaths by NCDs are double than that resulting from a combination of infectious diseases (including HIV/AIDS, tuberculosis and malaria), maternal and perinatal conditions, and nutritional deficiencies, and as a result 388 million people worldwide will die of one or more NCDs in the next 10 years (World Health Organisation, 2008a, Lopez A.D, 2006).

Two thirds (78%) of the deaths among older people occurred in LMIC, and in these regions too, chronic diseases are fast replacing communicable diseases as the leading causes of death and disability (Alzheimer's Disease International, 2009). Of the 35 million deaths in 2005 from NCDs, 80% occurred in LMIC (Fuster V, 2005). This is partly because most of the world's older people live in these regions - 60% now rising to 80% by 2050. There is therefore a growing interest to put chronic diseases on global and national agendas. However, mental health and particularly dementias remain a low priority in most low and middle income countries. The Sixty-sixth General United Nations special assembly meeting on chronic disease prioritizes ischaemic heart disease, stroke, diabetes and cancer - dementia was not considered a priority (United Nations, 2011) . Nevertheless dementia is one of the most important contributors to disability and dependency in older people (Sousa et al, 2009). In addition, dementia can be a consequence of, or at least it is associated to other chronic vascular diseases, such as hypertension, diabetes, stroke and their risk factors (see section 1.3, page for details) .

I will therefore now consider in more details this neglected topic in developing countries.

1.2 Dementia

1.2.1 Prevalence of dementia

Dementia is a syndrome with a monumental impact on the quality of life of patients and their caregivers with a high societal cost. Primary dementias are currently incurable, and cause progressive, irreversible brain damage. They include Alzheimer's disease (AD) - the most common cause, vascular dementia, frontotemporal dementia and Dementia with Lewy Bodies. Dementia syndrome is characterized clinically by progressive decline in memory, executive function, language, and other areas of cognition, behavioural and psychological symptoms and the gradual loss of ability to perform all tasks of daily living.

There is a very relevant priority in the study of geographic variations in prevalence and incidence of dementia. The aetiology of most dementias is not completely understood, as well as the methods for their prevention. However, both prevalence and incidence of dementia are strongly age dependent. Hence, with the ageing of the population in regions such as Latin America, China and India, the magnitude of the dementia problem in the community is growing and presents a substantial health burden for the community. The study of geographic variation provides a potential opportunity to identify important risk factors for dementia, which may also be useful for prevention.

The EURODEM meta-analysis of dementia prevalence from 12 European studies carried out between 1980 and 1990 reported a general age- and gender-distribution similar for all studies across Europe (Hofman et al., 1991), suggested no significant geographic variation. The overall European prevalences for the five-year age groups from 60 to 94 years were 1.0, 1.4, 4.1, 5.7, 13.0, 21.6 and 32.2%, respectively. In those under 75 years the prevalence of dementia was slightly higher in men than in women; in those aged 75 years or over the prevalence was higher in women.

Ten years later Lobo et al (Lobo et al., 2000) compared, across studies, the age- and sex-specific prevalence of dementia and its main subtypes from 11 studies carried out in eight European countries reporting a 6.4 % age-standardized prevalence of dementia in Europe. The age pattern of the prevalence estimated seems to be stable in time, as there is a general similarity between the findings in his study and the results based on studies conducted the previous decade.

Studies from Nigeria (Hendrie et al., 1995b) and northern India (Chandra et al., 1998) suggested a much lower prevalence (a quarter) of both dementia and the Alzheimer's disease subtype than that observed in the European meta-analysis. The overall age-adjusted prevalence rates of dementia and Alzheimer's disease in Ibadan, Nigeria were 2.3% and 1.4%, respectively. The rural India study showed overall dementia prevalence of 1.4% and 1.1% for Alzheimer's disease in the population aged 65 years and older.

In 2005, an expert consensus group (Ferri et al., 2005) estimated age-specific dementia prevalence for different world regions, based on published evidence, using the Delphi

technique. Consensus estimates supported a lower prevalence of dementia in developing regions than in developed regions, particularly in sub-Saharan Africa and in south Asia compared with other regions.

In 2009 the World Alzheimer Report (Alzheimer's Disease International, 2009) a new systematic review of the global prevalence of dementia, identifying 147 studies in 21 Global Burden of Disease (GBD) world regions, the accumulated evidence suggested quite similar age-standardised prevalence worldwide, with the possible exception of sub-Saharan Africa. After that, three studies in Sub Saharan Africa reported a much higher dementia prevalence than that reported in the Ibadan Nigeria study (Hendrie et al., 1995b) which was much more similar to those find in high income countries (HIC). In a study conducted in central Nigeria with a stratified, random community sample of 280 persons aged 65 years and older, prevalence of dementia was reported to be 6.4% overall (Ochayi et al., 2006) and another study conducted a door-to-door surveys in elderly living in two urban cities of Central Africa and estimated a prevalence dementia of 8.1% (95% CI , 5.8–10.8) in Bangui (Republic of Central Africa) and 6.7% (95% CI, 4.7–9.2) in Brazzaville (Congo) (Guerchet M et al, 2010) .

Two studies , one in a rural area of Benin (Guerche M et al., 2009) reported a 2.6 % prevalence of dementia similar to that reported by Hendrie et al (Hendrie et al., 1995b) in Nigeria. The other study was cross-sectional (Paraïso M et al., 2011) and included 1,162 people aged 65 and over who had lived in an urban area of Benin and found an overall prevalence of dementia of 3.7% (95% CI 2.6–4.8) slightly higher than it was

found in a rural area, but still close to that recorded in Ibadan study of 2.3% (95% CI 1.2–3.4) overall.

Although estimates of dementia prevalence might be similar in many parts of the world, the absolute number of people with dementia is much higher in LMIC compared to HIC. Ferri et al (Ferri et al., 2005) based upon systematic review of prevalence data and expert consensus, estimated that not only 24.2 million people live with dementia worldwide but also that there are 4.6 million new cases annually (similar to the annual global incidence of non-fatal stroke). The majority of people with dementia live in low and middle income countries (LAMIC), 60% in 2001 rising to 71% by 2040. Increases to 2040 will be much sharper in developing (300%) than in developed regions (100%) (The 10/66 Dementia Research Group, 2000a).

The World Alzheimer Report 2009 estimated that absolute numbers are even higher than the previous review; 35.6 million people with dementia, the numbers nearly doubling every 20 years, to 65.7 million in 2030 and 115.4 million in 2050 (Alzheimer's Disease International, 2009). These new estimates based in a large number of new studies, particularly from low and middle income countries provide more robust and valid figures based on quantitative meta-analyses in 11 of the 21 GBD world regions and not only on expert consensus as previous ADI estimates, published in 2005 (Ferri et al., 2005). Most of the increase in numbers is explained by the different base year for the estimates (2010 versus 2001). Like for like comparison indicates that the new numbers are 10% higher than those from the previous Delphi consensus. Compared with the earlier Lancet/ADI consensus estimates those for three regions were higher - Western

Europe (7.29% vs. 5.92%), South Asia (5.65% vs. 3.40%) and Latin America (8.50% vs. 7.25%). Those for East Asia were lower (4.98% vs. 6.46%).

The World Alzheimer's Report (Alzheimer's Disease International, 2009) estimated 3.4 million people living with dementia in Latin America in 2010, increasing to 7.7 millions in 2030. Estimated numbers of people with dementia in Cuba are 130 000 in 2010, doubling to 260 000 by 2030 (Llibre Rodríguez J, 2008).

In the most recent database search and meta-analysis in Latin American (LA) region (Nitrini et al., 2004), Nitrini et al., describes a regional dementia prevalence rate of 7.1% (CI 6.8-7.4%). This group reported slightly higher rates for women compared to men in all age groups, a similar finding to that was reported in the 10/66 Dementia research Group studies five Latin American countries using the same methodology (Llibre Rodríguez, *et al*, 2008). However, a limitation of the Nitrini et al. meta-analysis is that the constituent studies used different study design and diagnostic criteria. In the systematic review conducted for the 2009 World Alzheimer report using Western Europe as the standard population, the highest standardised prevalence for any world region (aged 60 and over) was observed in Latin America (8.5%) (Alzheimer's Disease International, 2009).

1.2.2 Incidence of dementia

Studies on the incidence of dementia are much less common than prevalence studies partially because of the considerable resources and time required. Several studies have been published on the incidence of dementia and Alzheimer's disease in HIC countries; Sweden (Hagnell O et al.,1992; Aevansson O and Skoog I.,1996; Fratiglioni L et.al, 1997), Finland (Mo'lsa' PK et al., 1982.), Germany (Fichter MM et al., 1996.), United Kingdom (Copeland, Davidson, Dewey, *et al*, 1992; Matthews F, Brayne C & Medical Research Council Cognitive Function and Ageing Study Investigators, 2005b), the Netherlands,(Ott et al., 1998a), France (Letenneur et al., 1993), the United States (Bachman et al., 1992), and Japan (Fukunishi I et al., 1991). Only a few studies have been conducted in LMIC, which, generally, report lower incidence rates compared to HIC (Chandra *et al*, 2001; Hendrie *et al*, 2001; Li *et al*, 1991; Nitrini *et al*, 2004).

In 1998 Jorm et al (Jorm and Jolley, 1998) analysed data from 23 published studies reporting age-specific incidence data, and they found that the incidence of dementia rises exponentially to the age of 90 years. East Asian countries had a lower incidence of dementia and AD than Europe and the United States. The annual incidence rates reported in the EURODEM metaanalysis (Fratiglioni et al., 2000) are roughly one-quarter of the point prevalence suggesting an average disease duration (from onset to death) of four years.

According to the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS)(Matthews F et al., 2005), the largest UK-based multicentre study into functional and cognitive health of the elderly, the population burden of the incidence of dementia equates to approximately 180,000 newly occurring dementia cases each year in England and Wales (95% confidence interval [CI], 105,000 to 325,000). In the Canadian Health and Aging Study the overall age-standardized incidence rates were 21.8 (women) and 19.1 (men) per 1,000 nondemented persons per year. This means 60,150 new cases of dementia per year in Canada.

In the single longitudinal study carried out in Latin America, the Catanduva Study in Brazil (Nitrini et al., 2004), with 50 incident cases and 3,623 person years of follow-up the incidence rate of dementia was 13.8 per 1000 person-years for individuals aged 65 years or older, considerably lower than those from North American and European countries.

Ferri et al (Ferri et al., 2005) reported a global incidence of dementia in 7.5 per 1000 person years for those aged 60 and over, equating to 4.6 million new dementia cases per year, similar to the incidence of non-fatal stroke. Meanwhile, the annual regional dementia incidence rates (per 1,000 individuals in the population) were estimated to be 10.5 for North America, 8.8 for Western Europe, 9.2 for Latin America, and 8.0 for China and its western-Pacific neighbours. The lowest annual incidences were estimated for India and South Asia, 4.3/1000 and Africa Sub-Saharan 3.5/1000. (Ferri et al., 2005). Incidence was estimated from the Delphi consensus prevalence and mortality using The

Global Burden of Disease project DISMOD-II software developed by WHO (Barendregt JJ et al., 2003).

1.2.3 Methodological issues regarding prevalence and incidence of dementia

Epidemiological research on dementia in developing countries, and also the impact of cardiovascular risk factors such as hypertension, type 2 diabetes and obesity, diet and lifestyle that may increase the risk for dementia and AD, are scarce, with very little available information (Fuster V, 2005, Yusuf et al., 2001b).

Many studies have reported that prevalence of dementia is lower in developing countries than in the developed north (The 10/66 Dementia Research Group, 2000a, The 10/66 Dementia Research Group, 2000b), strikingly so in some studies (Chandra *et al*, 1998; Hendrie *et al*, 1995). ADI's expert consensus panel, reviewing all available evidence, confirmed this trend (Ferri et al., 2005), which seems not to be explained by differences in survival (Chandra *et al*, 2001; Hendrie *et al*, 2001).

If there is regional variation in the prevalence and incidence of dementia, and this difference is real, rather than a methodological artifact, and if they can be confidently attributed to underlying real differences in disease incidence, it will be of particular importance for policy to understand the influence of the genetic and/ or environmental aetiology. If environmental, we need to identify the adverse exposures so we can control

them; if genetic, then identification of the genes responsible might elucidate pathological mechanisms and suggest specific therapies.

Geographical variation might indicate differences in population levels of exposure to environmental risk factor and lifestyle, such as low levels of cardiovascular risk (Hendrie *et al*, 2004) and hyperlipidaemia (Breteler and Hofman, 1998 , Chandra and Pandav, 1998) in some developing countries. However, other potential risk exposures will be more prevalent in LMIC, for example low education, anaemia, which was found to be associated with AD in rural India (Pandav *et al.*, 2004). Regional variation could also be genetic or arise as a result of interaction between genes and environment.

Methodological differences can also account for differences in disease frequency between LMIC and HIC studies. I describe some of the most relevant aspects related to the quality of epidemiological studies on dementia field.

1.2.3.1 Study Design

One of the most significant current discussions in prevalence and incidence phase studies is related to the study design (one or two stage design). Overall, 70% of dementia prevalence studies assessed in the systematic review carried out for the 2009 World Alzheimer Report used a multiphase survey design because of perceived efficiencies in interviewer time and cost (Alzheimer's Disease International, 2009) . In the standard two-stage method for dementia diagnosis, cognitive screening instruments exclude most people who do not have dementia. Attrition is generally marked between the first and

second phase (The 10/66 Dementia Research Group, 2000b); participants with probable dementia are particularly likely to refuse, to move away or to die, leading to informative censoring. The problem is compounded when no random sample of screen negatives is selected for second phase assessment (Prince, 2003, Prince, 2001, Dunn et al., 1999), as was the case with several previous studies from the Latin American region (Llibre Rodriguez et al., 2008c, Nitrini et al., 2009).

1.2.3.2 Sample size

A study of 500 participants could estimate a true prevalence of 6% with a precision of $\pm 2.1\%$. Precision increases to $\pm 1.2\%$ for a sample size of 1500 and to $\pm 0.8\%$ for a sample size of 3000 (Alzheimer's Disease International, 2009). In general, sample sizes tended to be larger in LMIC studies, but in the particular case of African studies, there are difference in the sample size from those who reported low and higher prevalences of dementia, for example in the study from central Nigeria reporting a higher prevalence of dementia the sample size was fewer than 300 older people (Ochayi and Thacher, 2006).

1.2.3.3 Diagnostic Criteria

Erkinjuntti et al (Erkinjuntti et al., 1997) examined the effects of six commonly used classification schemes — those of the third edition of the DSM (DSM-III) (American Psychiatric Association, 1980), the DSM-III-R (American Psychiatric Association, 1987), the fourth edition of the DSM (DSM-IV) (American Psychiatric Association, 1994), the ninth edition of the ICD (World Health Organization, 1978), the ICD-10

(World Health Organization, 1992), and CAMDEX (Roth et al., 1986) on the prevalence of dementia in the Canadian study of Health and Aging (CSHA), a population-based cohort of older people. In this report the proportion with dementia varied from 3.1% when ICD-10 criteria were used to 29.1% when the DSM-III criteria were used. The factors that most influenced diagnostic differences were long-term memory, executive function, and the duration of cognitive symptoms. These findings together with the fact that the diagnosis of dementia in illiterate and low educated individuals is a difficult task and can erroneously increase the prevalence of dementia in this group, provides the need for validation of the criteria used for diagnosing dementia.

Prince (2008) draws our attention to the lack of operational definition as the main weakness of DSM-IV. What constitutes memory impairment, or cognitive disturbance? What is a significant impairment in functioning? What represents a significant decline in functioning? When is the disturbance better accounted for by another axis one disorder? (Prince *et al*, 2008). Reisberg (Barry R, 2006) listed additional critiques related to DSM-IV criteria. Firstly, prominent dementing diseases such as vascular dementia and frontotemporal dementia (FTD) are characteristically not marked by impairment of memory (Neary D, 1998; O'Brien JT, 2003). Hence, by any criterion, including internal consistency as well as external validity, impairment in memory should not be a necessary criterion for a dementia diagnosis. Secondly, the omission on dementia definition of functional (ie, the ability to carry out activities) or behavioral/emotional changes and dementia is characterized by multiple cognitive deficits, functional deficits, and, commonly, behavioral/personality changes. For instance, FTD is characterized by

prominent behavioral and psychological symptoms during dementia presentation and course.

Finally, differences in prevalence across studies might also be due to different interpretation and application of common diagnostic criteria. To illustrate this point the DSM-IV dementia criterion might substantially underestimate the true prevalence of dementia, especially in least developed regions, because of difficulties in defining and ascertaining decline in intellectual function and its consequences.

1.2.3.4 The scope of dementia diagnosis assessment

A dementia diagnosis requires the existence of the following criteria: cognitive impairment (and decline from a previous level of functioning) in memory and other domains of intellectual function, and consequent social or occupational impairment and the exclusion of other causes of cognitive impairment such as functional psychosis, depression and delirium. Only 43% of studies from the systematic review carried out for the World Alzheimer Report 2009 included multidomain cognitive testing, functional assessment, clinical interview and informant interview. Informant interviews were most likely to be omitted.

This is an important issue in developing countries where, low levels of education, literacy, and numeracy can result in cognitively unimpaired people screening positive for dementia.

1.2.3.5 The used of standardized procedures that are culturally sensitive and the established criteria for the diagnosis of dementia

In 2003, Prince and co workers develop a methodology (the 10/66 Dementia diagnostic algorithm) for culturally and educationally sensitive dementia diagnosis in clinical and population-based research (Prince et al., 2003). Later as part of this development/validation exercise this dementia algorithm assessments was also validated in Cuba against a local clinician DSM-IV diagnosis and the 10/66 dementia diagnosis. Agreement with the clinician diagnosis was better for 10/66 dementia (Kappa 0.79) [95 % CI 0.74-0.83] than for the DSM-IV computerized algorithm (Kappa 0.63) [95 % CI 0.56-0.69] (Prince *et al*, 2008). The 10/66 dementia diagnosis defines a broader category that may be more sensitive, identifying genuine cases beyond those defined by the DSM-IV algorithm. In 2008 we published a paper, which is part of the analysis proposed in this essay (Llibre Rodriguez *et al*, 2008) where we compared the 10/66 diagnosis against the DSM-IV. Using the data from the population based studies in Latin America, China and India we were able to show that DSM-IV criteria consistently underestimate the proportion of people with dementia, compared with 10/66 mild, moderate and severe (Llibre Rodriguez *et al*, 2008).

1.2.4 Impact of dementia

Dementia is a disorder with a significant impact upon:

1. The person with dementia who experiences marked disability, severe impairment of quality of life and reduced life expectancy (Alzheimer's Disease International, 2009).
2. Family and caregivers who, experience adverse psychological, physical, social, and financial consequences, (Brodaty H et al., 2003; Max W et al., 1995) such as higher levels of anxiety and depression, (Rosenthal CJ et al., 1993) deterioration in physical health, (Schulz R et al., 1990) social isolation, (Brodaty and Hadzi-Pavlovic, 1990) and direct (e.g., medications) and indirect (e.g., loss of earnings due to relinquishing of paid work) financial costs. Caregivers (CG) are crucial for maintaining people affected with dementia in the community, decreasing the likelihood of nursing home admission (Brodaty et al., 1993).
3. The society, supporting the cost of providing health and social care and the opportunity cost of lost productivity (Alzheimer's Disease International, 2010).

According to the Global Burden of Disease (GBD) estimates for 2004, 68% of the 751 million years lived with disability (YLD) worldwide are attributable to chronic non communicable diseases, and 84% of this burden of chronic-disease disability arises in countries with low and middle incomes (Lopez A.D, 2006). Dementia is one of the main contributor to years lived with disability in persons aged ≥ 60 years, accounting for 11.2% - surpassing stroke (9.5%), musculoskeletal diseases (8.9%), cardiovascular disease (5.0%) and cancer (2.4%) (Lopez A.D, 2006; Alzheimer's Disease International, 2009).

Dementia accounts for 4.1% of total disease burden (Disability Adjusted Life Years) among people aged 60 years and over, 11.9 % of years lived with disability and 1.1 % of years of life lost. Heart disease (32.9% of years of life lost) and cancer (22.5%) are the leading causes of death, nevertheless, these are only 8th and 9th in the rank of disabling conditions, however dementia is the second burdensome among the other chronic condition. (Alzheimer's Disease International, 2009).

The 10/66 Dementia Research Group (Sousa *et al*, 2009) analysed the data from catchment area sites in seven countries with low and middle incomes and concluded that dementia was overwhelmingly and consistently the largest contributor to disability in elderly people. Sensory impairment, both of eyesight and hearing, and heart disease contributed much less to disability than suggested by the GBD.

According to the World Alzheimer Report 2010 the total estimated worldwide costs of dementia are US\$604 billion in 2010 (Alzheimer's Disease International, 2010). Approximately 70% of the costs occur in Western Europe and North America. Costs were attributed to informal care (unpaid care provided by family and others), direct costs of social care (provided by community care professionals, and in residential home settings) and the direct costs of medical care (the costs of treating dementia and other conditions in primary and secondary care). As the number of persons with dementia doubles every 20 years, costs can be expected to rise proportionately.

This financial burden, combined with the challenge of growing numbers of frail dependent older people, will produce dramatic changes in health systems and social care needs should also be a matter of great concern for policymakers in LMIC.

1.3 Why Study Dementia In Cuba

1.3.1 Origin of Cuban population

The history of admixture in Cuba began when Europeans came for the first time to Cuba in 1492. When Christopher Columbus arrived to Cuba in 1492, two different Native American groups inhabited the island: the Ciboneys, extending across the whole island, and the Tainos, mainly occupying the Central and Eastern regions of Cuba (Dacal-Moure and Rivero de la Calle, 1986). The Caribbean was most likely populated by successive waves of migration originating from the Lower Orinoco Valley in South America, taking advantage of the close geographical proximity of the Caribbean islands.

The original Cuban Indian population, which consisted of approximately 100,000 individuals living in a neolithic society (Steward, 1949, Ortiz and Saco, 1932), was completely exterminated soon after the Spanish conquest beginning in 1510. This rapid disappearance, which took place in less than 30 years, was the result of epidemics, infant mortality, hunger, and collective suicides (Ortiz and Saco, 1932). Moreover, thousands of Indians were massacred at the beginning of the conquest in attempts by the Spanish to subjugate and later to break their resistance; in 1550 less than 5,000 had survived (Perez de la Riva J, 1972). At present roughly 500 Indians live in the most isolated mountains at the east region of the Island. The contribution, therefore, of the Indian population to the current Cuban gene pool is small so that the actual gene pool consists effectively only of African and European genes (Gonzalez et al., 1976, Mendizabal et al., 2008).

The importation of slaves from West Africa, the main sources for African slaves (Bight of Benin, North of Congo, Angola, the Bight of Biafra and Sierra Leone) and South-eastern Africa (Mozambique and Madagascar) began since the sixteenth century when more than 1,300,000 African slaves arrived to Cuba to work in the sugar plantations (Pérez de la Riva, 1979). Slavery was not abolished until 1886.

Immigration continued during the 18th and 19th centuries when Cuban institutions intensely promoted Spanish immigration, especially from the Canary Islands, but also from Cataluña, Andalucía, and Galicia reflecting fears of a growing African presence and the desire to "whiten" the Cuban population (Checa M, 2007). In addition between 1900 and 1930 close to a million Spaniards arrived from Spain. Also, Asian individuals, especially from Bengal and South China, arrived to Cuba to replace the slave labor force when slavery became illegal in the nineteenth century. After 1847 around 125,000 Chinese were reported to have arrived to the island to work in conditions of semi-slavery. (Le Riverend, 1967., Checa M, 2007).

Cuba was a Spanish colony for almost four centuries (1511–1898), with an economy based on agricultural and the exportation of sugar, coffee and tobacco to Europe and later to North America.

1.3.2 Demographics ageing and health indicators in Cuba

Cuba is a middle income country with health indicators similar to those of developed countries and a rapidly ageing population of 11.6 million. By the year 2020 Cuba will be the country in Latin America with the highest proportion of older adults (25% aged 60 years and over) (National Health Statistics, 2009, Ministry of Public Health, 2009). Despite its territorial homogeneity, the extent of demographic ageing varies between regions, with the proportion of people aged 60 and over varying from 9.6% in the municipalities of Moa in the province of Holguín to 25.4% in Plaza in the Havana City. The reduction of social and economic inequalities and implementation of better access to health service that occurred over the past six decades played a key role in the ageing process of the Cuban population. Health care is centrally planned and financed by the state. There is comprehensive coverage and free access; 99% of the population is registered with the catchment-area-organized family doctor system, with one doctor to every 160 households.

The life expectancy at birth is currently 78 years (76 for men and 80 for women), 1.1 million Cubans (10% of the population) are aged over 65 (Ministry of Public Health, 2009, National Health Statistics, 2009) and the proportion of those over 60 years is 16.6% and within this age group 17.4 % are aged 80 years and over (National Health Statistics, 2009). The life expectancy at age 60 years is 20.8 for men and 23.4 for women.

Nowdays the infant mortality rate is only 4.8 per 1000 live births, child survival rates continue to rise, with under-5 child survival at 99.4%, total fertility rate is low and stable (1.70 in 2009—well below the 2.2 required to assure generational replacement) According to estimates from the Cuba's National Statistics Office if current trends continue by 2030, 3.4 million Cubans will be 60 years and over, almost one-third of the population, becoming the oldest nation in Latin America and the Caribbean, and, by 2050, one of the 11 oldest countries in the world.(National Statistics Bureau, 2009; National Statistics Bureau , 2006).

However these rapid changes are having a serious effect in the National Health system. The prevalence of chronic non-communicable disease in the older population has generally increased over time, with consequent impacts on disability and needs for health service intervention and long term care. Health services, despite their high coverage, do no always meet the needs of older people. This is a challenge that the system is facing at the moment and will need to consider also at macro and micro levels of the society (Llibre J, 2011). In other words, there is an urgent need to approach to the paradox of the increase of life expectancy and the consequences determined by such processes as physical deterioration, reduced mobility, chronic illness, weakening or dysfunctional family, social networks, and psychological pressures in a particular social and economic context of a developing country where the demographic transition is taking place.

As with the majority of Latin American and Caribbean countries, chronic diseases are Cuba's number one health problem, causing 90% of all deaths, in order of frequency:

heart disease, cancer and cerebrovascular diseases, which together account for nearly 60% of all deaths.(Organización Panamericana de la Salud, 2008). In relation to risk factors, 32% of Cubans 18 years and over smoke, 47% of women and 37.6% of men are overweight or obese; 13% of children aged 1-14 years are overweight, 36.5% adults are physically inactive (45.1% in women; men 27.5%), 50% of Cuban adults consume alcoholic beverages; 7.7% drink heavily or are alcohol-dependent (Reed G, 2008).

1.3.3 Previous epidemiological research in dementia in Cuba

Like other developing countries the importance of studying the epidemiology and the impact of dementia in Cuba have grown in the last two decades as a result of concerns about the consequences of the rapid ageing process in the area. However, only a few studies have been conducted on the prevalence of dementia (Anzola-Perez *et al*, 1997; Llibre *et al*, 2009; Llibre *et al.*, 1999) and most were conducted in the west and central part of the Island.

The Pan American Health Organization (Anzola-Perez *et al.*, 1997) undertook one of the first study of the prevalence of dementia in Latin America. The study consisted of a cross-sectional examination of noninstitutionalized individuals 60 years of age and older in Buenos Aires (Argentina), Santiago (Chile) and Havana (Cuba). The study had a two-phase research design: a screening phase for the identification of persons with cognitive impairment and a confirmation phase for diagnosis of the presence of dementia.

In Cuba, four catchment area of the '10 de Octubre' municipality of the capital city of Havana were chosen and 1628 individuals randomly selected systematically in a multistage sample of city blocks. The Mini-Mental State Examination (MMSE) (Folstein et al., 1975), translated into Spanish was used for the diagnosis of cognitive impairment. The study only completed the first phase reporting a prevalence of 16% cognitively impaired in Havana, Cuba. As expected, lower scores of MMSE were seen in progressively older age-groups and among those with lower levels of education.

In 1998 I conducted a door to door two phase survey in 779 older people over 60 years in the municipality of Marianao and in a representative sample of 340 older from the semi rural area of Bauta, in the province of La Habana recruited by means of stratified sampling. The probable diagnosis of dementia syndrome or Alzheimer's disease was based on criteria of DSM III R (American Psychiatric Association, 1987) and NINCDS-ADRDA criteria (McKhann et al., 1984). We found a dementia prevalence of 8.2% (CI 95% 6.3% to 10.4%) and that of Alzheimer's disease and vascular dementia was 5.1% and 1.9% respectively (Llibre et al., 1999).

One of the most extensive studies of dementia and Alzheimer's disease in Cuban and Latin American populations is The Disability and Alzheimer's disease Playa Study (EDAP) (Llibre et al., 2009). It was a two-phase, cross-sectional, door-to-door, study conducted in the Playa Municipality of Havana City from September through December, 2003, to ascertain and characterize the behavior of Alzheimer's disease and other dementias, as well as associated risk factors, in residents aged ≥ 65 years. The response

rate was a 96.4% (n= 18,351). Folstein Mini Mental State Examination (MMSE) (Folstein et al., 1975), Hughes Clinical Dementia Rating (Morris JC, 1993) and a structured interview on risk factors were applied. DSM –IV (American Psychiatric Association, 1994), NICDS-ARDRA (McKhann et al., 1984) and NICDS-AIREN criteria (Roman GC et al., 1993) were used to determine dementia diagnosis, as well as other criteria for diagnosing Alzheimer's and other specific forms of dementia. Dementia prevalence was 8.2% of adults aged ≥ 65 year, with a slight predominance in males. The most frequent cause of dementia was Alzheimer's disease, followed by mixed dementias. The dementia-associated risk factors were: history of stroke, arterial hypertension, depression, head trauma, family history of dementia, low educational level and advanced age.

In another Cuban population community study, a door-to-door study was conducted from January through March 2004 in Santa Clara Municipality (located in the central part of the island), using the same design as the EDAP in Havana. A total of 20,064 adults aged ≥ 65 years were surveyed (93.1% response rate), and a dementia prevalence of 7.1% (95% CI: 6.7%–7.5%) was reported, with a predominance among women. (Llibre Rodríguez J, 2008). Both studies have already drawn attention to the high prevalence of dementia in Cuba.

Some studies exist of the prevalence of dementia in older Cubans living in USA. One of them, the South Florida Program on Aging and Health (Demirovic J et al., 2003) a cross-sectional community-based epidemiologic study conducted between 1993–1997, examined a population sample of 2,759 elderly (65 years of age and older) African

American, Hispanic-Cuban and white non-Hispanic men and women of Dade County, Florida, 36 % of the sample, 990 people were white Hispanic born in Cuba (374 men and 616 women). The prevalence of cognitive impairment for African American men was 17.0% and women 16.7%; Cuban men 9.4% and women 11.4%; and white non-Hispanic men 9.0% and women 8.5% .There are a few more methodological considerations of importance in interpreting results of this study. The cross-sectional design has its limits in ascertaining a diagnosis of dementia from a one-time clinical evaluation and also the low response rate of participants who were referred to clinical evaluation limits validity of the results.

Sevush et al.(Sevush et al., 2000) studied the risk for AD conferred by APOE4 in 145 patients with AD (80 Cuban American and 65 white non-Hispanic) and 49 control subjects (21 Cuban American and 28 white non-Hispanic) living in South Florida and reported that the relative risk of AD conferred by the Apo-E e4 allele was somewhat greater for Cuban Americans (OR 4.33; range: 1.27–14.79) than for white non-Hispanics (OR 3.40; range: 1.48–7.79), but the difference was not statistically significant ($p < 0.1$).

1.4 Environmental Risk Factors For Dementia

1.4.1 Cardiovascular risk factors

Epidemiological studies have been suggested, that up to 50% of dementia might be preventable (Barnes and Yaffe K, 2011, Jansson E.T, 2005). As age itself is the strongest determinant of dementia, an intervention should be regarded as effective if disease onset can be postponed. Research suggests that vascular disease predisposes to AD as well as to vascular dementia (Hofman et al., 1997) . There is a strong evidence base from epidemiological cohort studies suggesting a causal role for cardiovascular risk factors (CVD) in the aetiology of dementia and AD (Barnes and Yaffe K, 2011, Hughes T and Ganguli M, 2009). Nevertheless, evidence for the associations between vascular conditions and dementia suggests stronger risk estimates for midlife compared to late-life exposures (Kloppenburg RP et al., 2008).

In fact few studies have examined the impact of risk factors with exposures more than a few years prior to dementia onset, which does not permit discrimination between a true independent risk factor and a prodromal or early symptom. Ideally, a life course approach is needed to study risk factors and identify prevention opportunities for dementia.

Life course epidemiology is defined as “the study of long term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood and later adult life” (Kuh D et al., 2003). This model takes into consideration both the temporal order of risk factors and their interrelationships,

including gene-environment and environment-environment interactions. Using this approach, epidemiologist must begin to examine risk factors starting not only a few years before clinical onset of dementia, even several decades earlier.

I would like to mention some of the most important vascular risk factors that have been described in the context of dementia.

1.4.1.1 Blood Pressure

In general evidence in support of an association between hypertension and dementia suggests that it varies according to the time that the exposure is measured, where high blood pressure in midlife is associated with mild cognitive impairment (Kivipelto M *et al.*, 2001) and increased risk of dementia (Whitmer *et al.*, 2005 ; Yamada M *et al.*, 2003) (Kivipelto M *et al.*, 2002; Kivipelto M *et al.*, 2005; Launer LJ *et al.*, 2000), but in late life is associated with a reduced risk of dementia (Guo Z *et al.*, 1996; Ruitenberg A *et al.*, 2001).

As hypertension decreases the vascular integrity of the blood-brain barrier (BBB), resulting in protein extravasation into brain tissue.(Kalaria, 2010), this can lead to cell damage, a reduction in neuronal or synaptic function, apoptosis, and an increase in A β accumulation, resulting in cognitive impairment. The association between high blood pressure and cerebrovascular disease neuropathology (infarcts, white matter lesions) may also contribute.

1.4.1.2 Smoking

In short (Juan, *et al*, 2004; Luchsinger *et al*, 2005; Ott *et al*, 1999) and longer latency (Rusanen M *et al*, 2010.; Tyas *et al*, 2003; Whitmer *et al*, 2005) incidence studies, smoking increases the risk for Alzheimer's disease. In longitudinal studies without tobacco industry-affiliated authors the RR for AD among smokers was 1.45 (1.16–1.80) (Cataldo JK *et al.*, 2010). The plausible mechanism including the increasing of the generation of free radicals, leading to high oxidative stress, and also inflammatory immune system, leading to activation of phagocytes and further oxidative damage.(Traber *et al.*, 2000). In addition, smoking may promote cerebrovascular disease.

1.4.1.3 Diabetes Mellitus

In observational studies Type 2 Diabetes has been shown to be associated with an almost two-fold increased risk of AD. (Leibson 1997; Luchsinger *et al*, 2001; Ott *et al*, 1999). A meta-analysis conducted by Lu and colleagues (Lu FP *et al.*, 2009) analysed eight prospective population based studies reported a RR of 1.47 (1.25–1.73) for all-cause dementia combined.

Diabetes and impairment of glucose tolerance lead to the formation of advanced glycosylation end products (AGEs), and amyloid plaques and NFTs contain receptors for AGEs (RAGEs), which also could be implicated in the neuronal damage caused by A β ,31.(Reitz *et al.*, 2011)

1.4.1.4 Obesity

The association of body weight with the risk of AD seems to depend on the age at which body weight is measured (Gustafson *et al*, 2003; Razay & Vreugdenhil, 2005; Stewart *et al*, 2005). Studies that have analysed overweight or obesity in midlife and the risk of dementia or AD have overall found an increased risk (Gustafson D *et al*, 2003; Kivipelto M *et al*, 2005; Rosengren A *et al*, 2005; Whitmer RA *et al*, 2005a; Whitmer RA *et al*, 2007). However there is an inverse association between adiposity in late-life and risk for AD (Atti AR *et al*, 2008; Sturman MT *et al*, 2008).

Profenno and colleagues in a recent meta-analysis that included six studies on obesity and AD have reported a RR 1.59, (95% CI 1.02–2.48) for the association between obesity and AD (Profenno LA *et al*., 2010).

As midlife overweight or obesity increase the risk of hypertension, diabetes, and hypercholesterolemia it seems to be the most obvious mechanism by which obesity may increase the risk of dementia in late life. An attractive explanation considers the effects of adipose tissue, which is metabolically active endocrine tissue that secretes several proinflammatory cytokines, hormones, and growth factors that cross the blood-brain barrier and affect brain health (Gustafson, 2006b; Rosengren A *et al*, 2005; Whitmer RA *et al*, 2005b; Whitmer RA *et al*, 2007)

1.4.1.5 Cholesterol

The best explanation for the inconsistent findings on the association on cholesterol level and dementia seems to be the timing of cholesterol measurement in relation to the time

of dementia onset. Similar to body weight and blood pressure, high total cholesterol in midlife may be associated with an increased risk of cognitive impairment (Solomon A et al., 2007) and dementia (Panza F et al., 2006;) and AD (Kivipelto et al, 2005; Mielke MM et al, 2005), while high late-life cholesterol may not affect risk (Reitz C, 2008; Tan ZS, 2003) or be associated with lower risk (Mielke MM et al., 2005). In addition, recent studies have shown that cholesterol levels begin to decline before the onset of dementia and that more decline between mid- and late-life is associated with more severe cognitive impairment in late-life (Solomon A et al., 2007).

Evidence exists that depletion of membrane cholesterol inhibits secretase cleavage of APP, thereby lowering A β 1–40 and A β 1–42 accumulation (Pfeiger, 2003, Reitz et al., 2011). Nevertheless hyperlipidemia may also lead to atherosclerosis, which increases the risk of vascular disease, which in turn is associated with a greater risk of AD. The role that cholesterol plays in neuronal plasticity, (Pfeiger, 2003) or its antioxidant properties (Smith, 1991), or, a general wasting and loss of body mass associated with AD (Nourhashémi and Vellas, 2008;) may explain the association with higher late-life cholesterol and reduced risk of dementia in late life. The role of cholesterol in the pathology of dementia may also plausibly be linked with the role of the APOE genotype in lipid metabolism, as I will discuss later.

Recent studies report associations between metabolic syndrome and incident cognitive decline (Yaffe et al., 2004), and insulin resistance and impaired executive function (Abbatecola et al., 2004).

Midlife obesity, midlife hypertension, and diabetes potentially contributed to a substantial proportion of cases of dementia and AD worldwide through vascular mechanisms, or production of substances that are important in metabolism (adipokines) and inflammation (cytokines) by adipose tissue and/or alternatively by insulin resistance and hyperinsulinaemia.

1.4.1.6 Cerebrovascular disease

Stroke is the third leading cause of death in the world (Strong K et al., 2007 , Feigin VL et al., 2009) with highest mortality in low- and middle-income countries. In a recent meta-analysis from 22 hospital-based and eight population-based cohorts Pendlebury and Rothwell concluded that 7.4% of patients with first-ever stroke developed poststroke dementia. (Pendlebury and Rothwell, 2009).

As stroke is strongly associated with cardiovascular risk factors and life style, several mechanisms could be explaining the association of stroke and dementia. First, stroke may produce a direct damage of brain regions that are related to cognitive function, such as the thalamus and the thalamocortical projections. In addition, stroke might increase A β deposition, which in turn can lead to cognitive decline. Finally, the onset of stroke may induce inflammatory responses that impair memory function.

1.4.2 Nutritional factors

In LMIC dietary deficiencies are common and strongly related to poverty. Deficiencies of folate and vitamin B12 and their consequences; anaemia, neuropathy, hyperhomocysteinaemia (Selhub et al., 1993), increased the risk of stroke and ischaemic heart disease (Robinson *et al*, 1998). Vitamin B12 deficiency is strikingly prevalent (> 40%) across Latin America (Allen, 2004; Arnaud *et al*, 2001; Garcia-Casal *et al*, 2005), linked to gastrointestinal infections and diets deficient in meat and dairy produce (Allen, 2004).

Folate deficiency is endemic in those living in poverty (Garcia-Casal et al., 2005), and after economic crisis (Arnaud et al., 2001). Diets deficient in legumes may also have contributed. Micronutrient deficiency is probably more prevalent in the older but there are few data on this age group (Harding, 2001). Iodine deficiency has also been a major public health problem in most Latin American countries (Pretell et al., 2004). Iodized salt is now generally available but iodine content is poorly regulated (Pretell et al., 2004). A prevalence of sub-clinical hypothyroidism of 16.1% was reported among post-menopausal Brazilian women (Petri Nahas et al., 2005).

1.5 Genetics of Dementia

1.5.1 The use of population admixture to understand the aetiology of chronic conditions

Having examined the role of the environmental factors, it is now necessary to consider the influence of admixture in epidemiological population studies. Genetics studies in admixtures population offer a unique opportunity to study the contributions of genes and environmental risk factors and their possible interaction to explain diseases rates in populations (Hendrie et al., 2004).

While a variety of definitions of the term ancestry has been suggested, this thesis will use the definition of biogeography ancestry, in which a person's origin is associated with the geographic location (s) of presumed ancestors inferred by comparison with contemporary population living in these locations (Royal C et al., 2010) .

It is also difficult to ignore that societal, ethical, moral and even political perceptions about ancestry guide that ancestry is seen or defined from personal or group interpretation of such identity or actual knowledge of genealogy.

The age-specific prevalence (Hendrie et al., 1995b) and incidence (Hendrie et al., 2001) of dementia in Nigeria are both very low. A further notable finding is the apparent lack

of an association between APOE genotype and dementia (Gureje et al., 2006), confirmed in Kenya (Kalaria et al., 1997). Those with African ancestry tend to have a higher prevalence of APOE ϵ 4, but African Americans, other populations of west African ancestry, and Hispanics, all show weak and inconsistent associations with AD (Farrer et al., 1997). There is a robust association between APOE genotype and AD in Europeans (Farrer et al., 1997) and south Asians (Ganguli et al., 2000).

Stewart (1999) reported that age and sex adjusted stroke incidence was higher among black (African Caribbean) residents, with a RR of 2.2 (1.8-2.8) using data from South London Stroke Register (Stewart et al., 1999). Findings concur with North Manhattan population-based incidence study: 2.4 times increase in stroke incidence in blacks compared to white people. In this community-based project, both relative risks and population attributable fractions varied across white, black and Hispanic ethnic groups for the major stroke risk factors (Sacco *et al*, 2001). In the USA the incidence of stroke was higher among African Americans and Hispanics (Sacco *et al*, 1998; White *et al*, 2005). These differences may be partly explained by elevated blood pressure levels (Chaturvedi, 2003). Conversely, African Caribbean migrants in the UK have a low risk of heart disease despite a high prevalence of metabolic syndrome, attributed to a low prevalence of smoking and low triglyceride levels (Chaturvedi, 2003).

Tang et al. (2001) comparing the incidence rates of newly diagnosed AD over a 7-year period from 1992 to 1999 in a community-based study of African-American, Caribbean Hispanic, and white older individuals residing in the communities in northern Manhattan, New York City (Tang M et al., 2001). In this study the incidence rate for AD

was significantly higher among African-American and Caribbean Hispanic older individuals compared white individuals at similar ages. The presence of clinically apparent cardiovascular or cerebrovascular disease did not contribute to the increased risk of disease. The majority (84%) of those identified as Hispanic were of Caribbean origin and 54% were from the Dominican Republic. The remaining individuals described as Hispanic were from Puerto Rico, Cuba, Mexico, and Central America.

Measurement of individual admixture proportions (the proportions of the individual's genome that are of African, European, and Native American ancestry) is now feasible, and studying the relationship of disease risk to admixture proportions is the most direct way to distinguish genetic from environmental explanations for ethnic variation in disease risk.

Those classified in the US as 'Hispanic' originate from diverse mixed ancestry Caribbean, Central and South American populations, resulting from two-way admixture between Native American and European populations or three-way admixture among Native American, European, and West African populations (Mao *et al*, 2007). However, patterns of admixture vary greatly among these populations. The catch-all 'Hispanic' category is therefore problematic, providing some information about linguistic and cultural heritage but very little about ancestry. In much of continental Latin America, two-way admixture dominates with little evidence of African ancestry (Wang *et al*, 2008). Cuba is quite different. the indigenous population was reputedly extinct by 1700, and Native American admixture is minimal (Cintado *et al.*, 2009). Importation of slaves from West Africa was current by 1600 and not abolished until 1886. In the 1832 census,

50% of the population was reported to be mulatto (mixed race) or black. Recent Cuban studies concur in identifying average proportions of African admixture in those who classify themselves as white, mixed race and black as, respectively, about 5%, 35% and 60% (Cintado *et al*, 2009). European admixture among African-Americans is much lower, an average of between 12% and 20% in different US cities (Parra et al., 1998) and very few African-Americans have as much as 50% European ancestry (McKeigue et al., 2000). In the former British Caribbean, average European admixture levels may be even lower; just 7% in Jamaica (Parra et al., 1998).

The high levels of African and European admixture in Cuba can be used to good effect. Studying the relationship of dementia risk to individual admixture within admixed populations is the most direct way to distinguish genetic from environmental explanations for ethnic differences in disease risk (McKeigue, 2005), and, by extension, for distinguishing gene by environment versus gene by gene explanations for ethnic differences in the effects of genes on disease outcomes. Furthermore, such relationships will confound studies of other genetic risk factors - “hidden population stratification”. Measurement of the confounder (individual admixture) allows us to control for population stratification using standard methods.

1.5.2 APOE and other genetic risk factors for dementia

The overall lifetime risk for AD in first-degree relatives of AD probands is about 38% by age 85 years (George-Hyslop., 2008). It has been suggested that genetic factors account for about 40% of the population risk for AD. In the majority of cases these genetic factors are manifest by the presence of multiple family members affected with AD (“multiplex pedigrees”) but without a clear cut mendelian pattern of inheritance. In his review about genetics of dementia George–Hyslop (2008) consider such cases of familial aggregated AD (FAD) likely reflect a complex mode of transmission such as: (1) one or more common independent, but incompletely penetrant, single, autosomal gene defects; (2) a multigenic trait; or (3) the effects of interaction between genetic and environmental factors (George-Hyslop., 2008).

The studies of molecular genetic in families with familiar early-onset of AD (EOFAD) have lead the discovery of three different genetic loci associated with a hereditary susceptibility to the autosomal dominant AD, namely APP (Precursor of the β Amyloid protein) itself codified by a gene located in chromosome 21, which are responsible for 2% of the total of cases of FAD and approximately 5-20% of early onset of the familiar Alzheimer disease (EOFAD) (Tanzi RE, 1996), and the presenilin genes (PSN1 and PSN2) genes located in the chromosomes 14 and 1 respectively, which encode proteins involved in APP breakdown and β A generation.. The mutations on PSN1 represents around 30-50% of the cases of FAD (Kalara RN, 1996). Nowadays around 182 different mutations have been discovered related to the gene of the presenilin 1 (Alzheimer

Disease & Frontotemporal Dementia Mutation Database, 2008). Only 14 AD- linked mutations have been identified in PSEN2, causing around 2% of the total of FAD, and occurring at a lower frequency than those found in gene PS-1 (Querfurth H.W, 2010).

In late onset sporadic as well as familial cases, which constitutes at least 95% of cases, the apolipoprotein E (APOE) gene on chromosome 19 has been identified as a major risk factor (Strittmatter et al., 1993a). In addition in 2009 Genome Wide Association Studies (GWAS), using a case-control methodology, identified three new genes related to the Alzheimer's disease of delayed onset, identified like - CLU (clusterin, also known like apolipoprotein J), PICALM (fosfatidil inositol together with the protein clathrin), and CR1 (component of the complement [3b/4b] of receiver 1). (Harold D, 2009; Lambert JC, 2009).

The human APOE protein is a 299 amino acid glycoprotein with variable levels of posttranslational sialylation through O-linked glycosylation at the threonine 194 residue. Apolipoprotein E (APOE) is a cholesterol transport protein which also takes part in the repair of injured nerves (Mahley, 1988). APOE is expressed in several organs, with the highest expression in the liver, followed by the brain. Nonneuronal cells, mainly astrocytes and to some extent microglia, are the major cell types that express APOE in the brain (Fagan, 1999; Pitas, 1987). In plasma, APOE proteins are present on lipoproteins in association with other apolipoproteins, whereas in the brain APOE and two other apolipoproteins, apoJ and apoA-1, are predominantly present on distinct high-density-like lipoprotein particles (Borgaonkar DS, 1993). APOE is polymorphic and

exists as three major isoforms referred to as apolipoprotein E2, E3 and E4. These are products of three alleles (e2, e3 and e4) at a single gene locus on chromosome 19.

The gene of APOE in humans contain three common polymorphisms: e2 (cysteine in codon 112 and codon 158), e3 (cysteine in codon 112 and arginine in codon 158), and e4 (arginine in codon 112 and 158). (Borgaonkar DS, 1993). The expression of any two of these three co dominant alleles results in three homozygous phenotypes (E2/E2, E3/E3, E4/E4) and three heterozygous phenotypes (E2/E3, E2/ E4, E3/E4) (Kim, 2009a).

The e4 allele of the apolipoprotein-E gene was first reported to be associated with an increased risk of AD twenty years ago (Saunders *et al*, 1993; Strittmatter *et al*, 1993). Since then, this has been the most consistently replicated genetic risk factor (Bertram *et al*, 2007). The presence of APOE e4 allele of the apolipoprotein-E gene (APOE e4) has been consistently associated with an increased risk of Alzheimer disease, but not all persons carrying the homozygous develop Alzheimer disease (AD) even when followed up to age 80 years and beyond (Borgaonkar DS, 1993; Mayeux R, 1993; Payami H, 1994a; Saunders *et al*, 1993; Strittmatter *et al*, 1993).

It has been proposed that the differential effects of APOE isoforms on β A aggregation and clearance play the major role in AD pathogenesis (Strittmatter *et al*, 1993b). Other potential mechanisms have not been ruled out, including the differential modulation of neurotoxicity and tau phosphorylation by APOE isoforms (Bertram L, 2010; Strittmatter *et al*, 1994) as well as its role in synaptic plasticity and neuroinflammation, or even the

possibility that the APOE $\epsilon 4$ allele alters the risk of dementia via changes in lipids metabolism and vascular disease (Poirier J, 1993; Roses AD, 1994).

This association seems to be affected by ethnicity, age, sex, medical history, and geographical location. Most of the observations report this association is less consistent for individuals > 80 years of age (Poirier J, 1993; Roses AD, 1994), may be stronger in women than in men (Payami H, 1994), and also differs between ethnic groups (Hendrie et al., 1995a). To illustrate this point APOE $\epsilon 4$ allele does not increase risk in sub-Saharan Africans and is only weakly associated with AD in Caribbean Hispanics and African Caribbean people of Jamaican origin (Farrer *et al*, 1997; Romas SN, 2002; Stewart *et al*, 2001). On the other hand, frequencies of the APOE $\epsilon 4$ allele are reported to be relatively increased in healthy Africans and some non-Africans: for example, 14–41% in indigenous people from Central African Republic, East Africa, Southern Africa, Malaysia, Australia, and Papua New Guinea, (Corbo RM, 1999; Kalaria *et al*, 1997; Sayi JG, 1997) compared with 8–12% in Caucasians and Japanese (Farrer et al., 1997).

Comparative analysis showed that the APOE $\epsilon 4$ allele was a risk factor for AD in African Americans, but not in Yoruba Nigerians (Gureje *et al*, 2006; Murrell JR, 2006) or in population samples from the Vihiga and Nyeri districts of Kenya (Kalaria et al., 1997) or Kingston, Jamaica (Morgan OS, 1998).

Early-onset familial AD in developed countries has not been reported to be modified by the APOE $\epsilon 4$ allele. However the APOE $\epsilon 4$ allele was strongly associated with late-onset familial AD among Caribbean Hispanics from the Dominican Republic and Puerto

Rico (Romas SN, 2002) but not in Guamanians with dementia. (Galasko D, 2007; Osuntokun *et al*, 1995).

Two longitudinal studies in the US also suggest no association between APOE e4 and incident AD among African Americans, while the incidence of AD seemed to be higher for African Americans in every APOE genotype (Evans *et al*, 2003; Sevush *et al*, 2000; Tang *et al*, 1998). In a case-control study in Florida the association between APOE e4 and AD was as strong for Cuban Americans as for white non-Hispanics (Sevush *et al*, 2000) in contrast to the absence of an observed association among Hispanics in North Manhattan (Tang *et al*, 1998).

In the only detailed population-based studies from sub-Saharan Africa, the prevalence and incidence of Alzheimer's Disease (AD) and dementia in Nigeria are very low (Hendrie *et al*, 2001; Hendrie *et al*, 1995). However, among African-Americans, prevalence and incidence seem to be similar (Hendrie *et al*, 2001; Hendrie *et al*, 1995), or even higher (Evans *et al*, 2003; Tang *et al*, 1998) than among white non-Hispanic Americans. Also, the prevalences of dementia in Caribbean and South American populations, including those where some degree of African ancestry can be quite common, are among the highest in the world (Llibre Rodriguez *et al*, 2008; Molero *et al*, 2007; Nitrini *et al*, 2009; Scazufca *et al*, 2008).

To summarise this section, the association between APOE and dementia has been observed in many different populations (Kalaria *et al*, 2008). So far, however, African-Americans, other populations of west African ancestry, and Hispanics show relatively

weak and inconsistent associations with AD, despite those with African ancestry tending to have a higher prevalence of the risk-conferring APOE e4 allele (Kalaria *et al*, 2008).

The weaker APOE4 association with dementia in populations with African ancestry, might be explain by genetics mechanisms First, there is a variation in APOE e4 alleles from population to population. These alleles may differ by nucleotide changes, which may affect gene function, or by nucleotide changes in the noncoding regions, which may affect gene expression (Fullerton et al., 2000, Hendrie et al., 2004). On the other hand, changes in nucleotide sequence in other genes that interact with APOE e4 (for example, apolipoprotein receptors) may affect function and, thus, affect the effect of APOE e4 as a risk factor for AD.

An alternative explanation could be that the lack of APOE e4 effect in people with high grades of admixtures is related to gene–environment interaction. The differences in cholesterol levels between sites and the role that APOE plays in cholesterol processing make an APOE–cholesterol interaction, resulting in a differential AD risk, an obvious possibility. Two previous studies have reported a significant interaction between APOE and cholesterol in determining risk for AD suggested that cholesterol mediates some of the effects of APOE e4 on AD (Notkola et al., 1998, Evans et al., 2000) (**see section 1.5.3**).

Epidemiologic studies on dementia in admixed population could provide us the oportunity to assess the role of genetic diversity and environmental factors in determining the prevalence and incidence of the disease in different populations. So far,

however, there has been little discussion about dementia in admixed populations living in Latin-Americans and Caribbean countries are still scarce in the continent.

1.5.3 APOE, lipids and dementia risk

Recent developments in the fields of epidemiological, clinical and pathological studies of sporadic Alzheimer's disease (AD) have led to a renewed interest in the relationships between a deterioration of brain lipid homeostasis and vascular changes in the pathophysiology of this disease. These associations include the epidemiological evidence that most risk factors for Alzheimer's disease are also related to vascular disease and premature death such as high midlife plasma cholesterol, diabetes, stroke, obesity and hypertension to dementia. Furthermore, the recognition of cholesterol transporters apolipoprotein E (APOE), APOC1 and APOJ as major genetic risk factors for sporadic AD support to the hypothesis that cholesterol has an important role in AD and is, therefore, a potential therapeutic target for disease prevention.

Cholesterol is a vital component of the central nervous system (CNS) and is essential for axonal growth, and synaptic formation and remodeling, processes that are crucial for learning, formation of memories and neuronal repair (Dietschy & Turley, 2004; Leduc et al., 2010). Lipids rafts – membrane microdomains rich in lipids and cholesterol – modulate APP processing. Consequently increased intracellular cholesterol levels, which favour lipid raft formation, negatively regulate α -secretase activity (Xiu et al., 2006,

Leduc et al., 2010) but stimulate both β -secretase, and γ -secretase activities, resulting in an increase in β A production.

However, epidemiological studies of serum cholesterol levels and risk of AD have been inconsistent. Some studies, including the Framingham study (Kivipelto *et al*, 2001; Notkola IL, 1998; Tan ZS, 2003) have suggested that elevation of serum total cholesterol, particularly in mid-life, increases risk of late cognitive impairment or dementia, but not others (Li, 2005; Slioter AJ, 1999; Wieringa GE, 1997) (see **section 1.3.1.5**). The Ibadan Indianapolis group has previously reported in 2000 a significant interaction between APOE e4, cholesterol, and AD in African Americans in whom increasing cholesterol levels increased the risk of AD in individuals without APOE e4 but not in individuals with the APOE e4 allele (Osuntokun et al., 1995). Prince et al. reported that the association between APOE and dementia does not seem to be mediated by cholesterol and others vascular factors (Prince M, 2000).

In 2006 Hall et al published a paper (Hall KS, 2006) in which they described a significant interaction between cholesterol, APOE e4, and the risk of Alzheimer disease (AD) in the Yoruba, a population that has lower cholesterol levels and lower incidence rates of AD compared to African Americans. Similar to cholesterol, they did observe an interaction between triglycerides and APOE genotype. In others words at low levels of triglycerides, possession of a e4 allele was associated with an increased risk of AD. In this study the sample size was too small (29 AD cases) to investigate the relationship of lipids, APOE and dementia. Another difficulty in the interpretation of the findings arose

from the cross-sectional design of the study, with the clear possibility that lipid levels may have been influenced by the onset of dementia.

1.6 Aims And Hypothesis

1.6.1 Aims

The main aims of this study was to describe the prevalence, incidence, correlates and impact of dementia among older Cubans; to assess the effects of reported ethnicity, admixture and Apolipoprotein E genotype on dementia prevalence and to estimate the association between cardiovascular risk factors and dementia incidence.

1.6.2 Objectives

The specific objects of the present study were:

- 1) Estimate the prevalence of dementia, incidence, correlates and impact of dementia in populations of older Cubans with high levels of African/ European admixture.
- 2) Assess the effects of ethnicity, admixture and Apolipoprotein E genotype on dementia prevalence.
 - a) Estimate the association between ethnic groups (defined by the interviewer) and individual admixture
 - b) Assess the association of each (ethnic group and individual admixture) with APOE genotype.

- c) Test the following hypotheses:
- i) the effect of APOE genotype on dementia is modified by ethno-racial group, and/ or admixture, with weaker associations among those with ‘mixed’ and ‘black’ ethno-racial identity and with higher proportions of African admixture
 - ii) the prevalence of dementia is lower among those with ‘mixed’ and ‘black’ ethno-racial identity, and is inversely linearly related to African admixture.
- 3) Assess the effect of cardiovascular risk factors on dementia incidence, testing the hypothesis that:
- i) Smoking, hypertension, diabetes, stroke, heavy alcohol use and hyperlipidaemia are associated with dementia incidence,
 - ii) the associations described in (i) are modified by APOE genotype, being stronger in APOE e4 carriers than-non-carriers.

CHAPTER 2 METHODS

2.1 Pilot Study

Before the cross-sectional study a preparatory study was conducted in 2003 in Havana to organize and plan the cross sectional survey and future follow-up

(i) we checked the registers of the family doctor service in a comprehensive catchment area to draw a representative sample of those aged 65 and over,

(ii) we identified the optimum procedures for carrying out participant and caregiver interviews, and

(iii) assessed the feasibility of obtaining prospective data on a variety of health-related exposures from six-monthly health checks carried out on all over 60 year old people assisted by their family doctors. Three family doctor areas (each covering a population of around 500 of whom around 40-50 should be aged 65+) were door-knocked to check the accuracy of the doctors' registers. This pilot showed excellent response rates both for interview and phlebotomy (98 %). Twenty people (and for each a suitable informant) were invited to undergo the full one stage dementia diagnosis interview. We also tested interviewers working in pairs; one to interview the participant and the other the informant; and assessed preferences for interviews in participants' homes, family doctors' surgeries and local polyclinics.

2.2 General Study Design, Setting and Sample

We conducted a one phase cross-sectional catchment area survey of all residents aged 65 years and over living in five urban districts in Havana, Cuba (Lisa, Luyano, Marianao, Playa, and Plaza); and one catchment area in Matanzas (Milanes), a port city 120 kilometers along the coast from Havana. In each municipality, polyclinics were selected purposively to ensure adequate numbers of older persons, an even distribution of admixture, and a history of health professionals previous participation in research.

A total of eight policlinics in Havana and one Policlinic from Matanzas were included. A door-knocking strategy was used to identify all possible eligible participants, and to allocate a unique identifier (HOUSEID) to each household. Each catchment area used in the door knocking strategy was delimited by including all household which were at a maximum distance of 500 meters from the Policlinics. For each household the gender and ages of all permanent residents were recorded with the name of those possibly or definitely aged 65 years or over on the census date. Age was formally ascertained and confirmed when the research workers returned to carry out the interview. Household and participants details were stored in secure databases which include names, addresses, and identifier (ID) number, and contact details for neighbours, key informant and friends to be used in the follow-up phase. For each participant an informant was identified to provide further information. The informant was chosen on the criteria either that they knew the participant best or had spent the longest period of time with the older person. Although in most cases they were co-resident of the older person and usually a family

member, in some cases a non co-resident family member, or friend or neighbour was better qualified.

A total sample of 3015 eligible participants were identified from which 2944 accepted and were interviewed (response proportion = 97.6%), 2043 in Havana (97.3%) and 901 in Matanzas (98.4%). Causes for non-response included refusal to participate in the study or failure to contact the person after five home visits.

An incidence phase was conducted from 2008 to 2010 with a median follow up of 4.5 years after the baseline interviews. From a total baseline sample of 2813, 608 (21.6%) were deceased, 178 could not be traced or contacted and 20 (0.7%) refused to participate. We could reinterview 2007 (71.3%). The cohort for the analyses of dementia incidence was defined as all those who were free of any dementia (either DSM-IV or 10/66 dementia) at baseline (n=2517). The proportions of the dementia-free cohort baseline who were found to be deceased was 17.8% (449), who refused, who could not be traced or contacted 176 (7.0%) , and who were successfully re interviewed, 1 892 (75.2%) (**See Figure 1**).

In order to explore the effects of ethno-racial identity and genetic admixture on APOE genotype, its association with dementia, and dementia prevalence a nested case-control study design was used with 235 dementia cases and a randomly selected sample of 349 participants without dementia (controls).

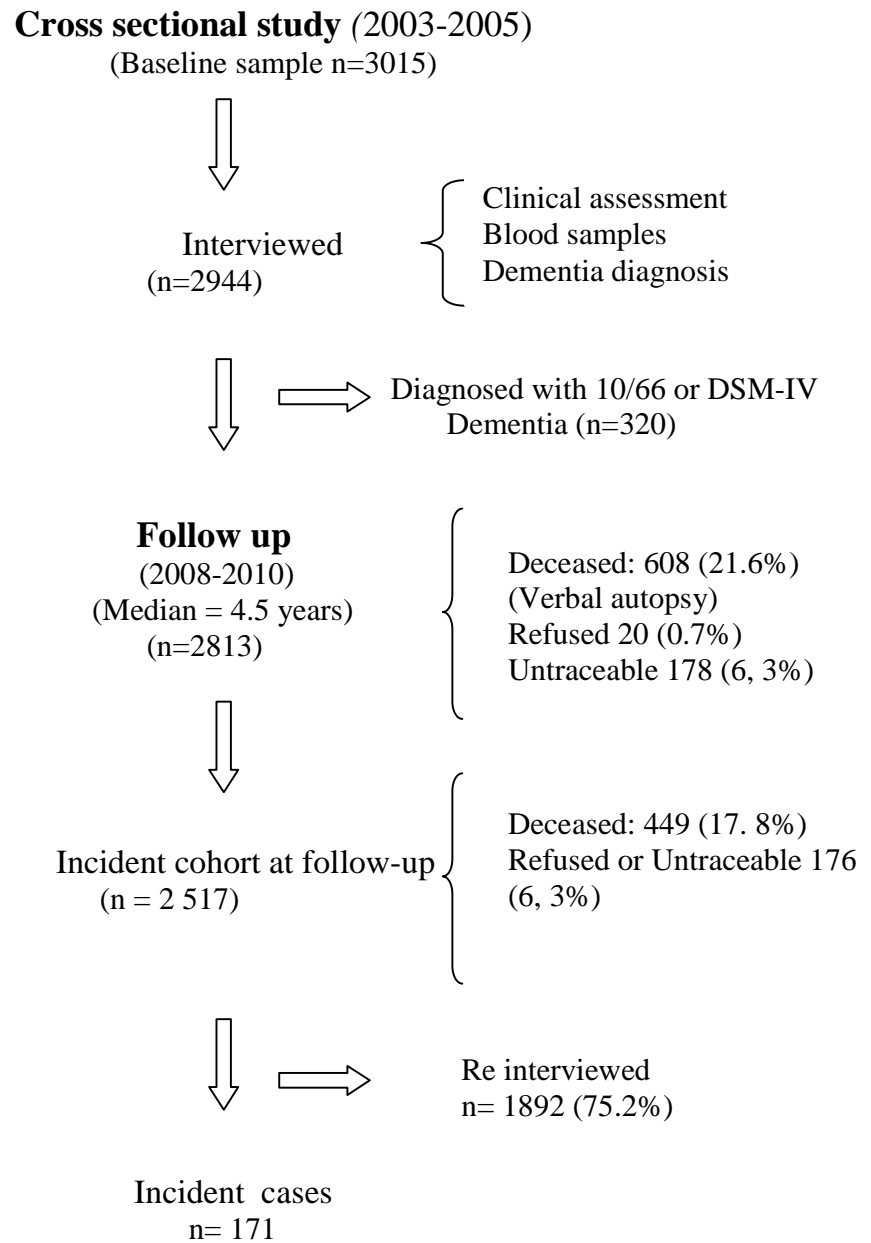


Figure 1. The Havana and Matanzas prevalence and incident study sample.

2.3 Preparation and Training

A total of 10 interviewers participated in a one- week planning meeting in order to standardize operating procedures according to the field manual as well as to train interviewers in the study protocol. All assessments were translated into Ibero-American Spanish with country-specific adaptations, where necessary.

I did the most of the quality control for the study and checked all questionnaires for completeness and coherence before data entry, supervised each interviewer in the field, conducting random checks every three weeks thereafter. The first and second supervisors (CPF and MP) visited the areas at least twice during the fieldwork phase.

2.4 Procedures

A door knocking of all eligible households were conducted to identify those age 65 and above. At this moment the full interview was scheduled for a convenient time for the participant and informant. The interviews were carried out in the participant's own homes.

The interviews were carried out by polyclinic doctors (five psychiatrists, two geriatricians and three general medical specialists) who worked in the Policlinics of the areas selected. . All interviewers had one week training to get the necessary skills in the general protocols and also in the Geriatric Mental State clinical assessment as well as the neurological/ physical examination.

All participants received a full assessment lasting approximately 2-3 hours, which included interviewing of participants, physical examination and phlebotomy, and an informant interview. Data were collected directly onto laptop computers using computerized Spanish questionnaires driven by Epidata software, including conditional skips and interactive checking.

Ethical issues – All participants were recruited on the basis of informed signed consent. Persons suffering from dementia who had no capacity for consent were recruited taking into consideration a relative's signed agreement. The information sheet and consent form, were read to illiterate people. They were also asked to express their consent verbally, which was be witnessed, but they were not asked to sign a form they could not read. Participants in the study were asked to offer a gift of genetic material (blood) to the local research institutions Medical University Havana) who acted as custodians and testified that the blood drawn from participants had a scientific purpose and not commercial. The Medical University of Havana, the National Centre of Medical Genetics (Cuba), and the Institute of Psychiatry institutional ethical committees reviewed and approved this project.

2.5 Measurements

The 10/66 population-based study interview generates information regarding dementia diagnosis and subtypes, mental disorders, physical health, anthropometry, demographics, an extensive non-communicable disease and dementia risk factor questionnaire, disability and functioning, health service utilization, care arrangements and caregiver strain. I will describe in details the measures which are relevant for this thesis. Further details of the protocol for the 10/66 Dementia Research Group programme are provided in an open-access online journal publication (Prince et al., 2007).

2.5.1 Outcome - The diagnosis of dementia

Dementia was diagnosed according to our own cross-culturally validated 10/66 dementia diagnosis algorithm (Prince et al., 2003) and according to DSM-IV criteria (American Psychiatric Association, 1994). A concurrent validation conducted in the course of the Cuban population-based study showed that DSM-IV dementia diagnosis was specific but less sensitive to mild to moderate dementia; the 10/66 Dementia diagnosis corresponded better to local clinician diagnosis and was more sensitive to these milder cases (Prince et al., 2008). The outcome for most of the analyses in this thesis is ‘any dementia diagnosis’ comprising all those meeting either or both of these criteria. Diagnoses were established following.

(i) A structured clinical interview, the Geriatric Mental State (GMS) version B3, which applies a computer algorithm (AGECAT – Automated Geriatric Examination for Computer Assisted Taxonomy) (Copeland et al., 1986), identifying organicity (probable dementia), depression, anxiety and psychosis and a single hierarchically determined diagnosis.

(ii) A cognitive test battery comprising a) the Community Screening Instrument for Dementia (CSI'D') COGSCORE (Hall et al., 1993) (incorporating the CERAD animal naming verbal fluency task), and b) the modified CERAD 10 word list learning task with delayed recall (Ganguli et al., 1996). The CSI 'D' consists of 20 minutes 32 item cognitive test administered to the participant and a 15 minute 26 item questionnaire administered to the informant, enquiring after the participant's daily functioning and general health (see iii below). The cognitive score (COGSCORE), is a summary score from the participant cognitive test with different weighting applied to different items.

(iii) An informant interview, the CSI'D' RELSCORE (Hall et al., 1993) for evidence of cognitive and functional decline, with additional information on dementia onset and course obtained from the modified (Dementia Diagnosis and Subtype) History and Aetiology Schedule (Dewey and Copeland, 2001). The discriminant function score (DFSCORE) combined the participant score (COGSCORE) and the informant score (RELSCORE) into a single score.

(iv) The adapted CERAD ten word list learning task was developed in the Indo-US Ballabgarh dementia study (Ganguli et al., 1996). Six English words were taken from

the original CERAD battery list: butter, arm, letter, queen, ticket, and grass. The remaining four (pole, shore, cabin, and engine) were replaced with corner, stone, back, and stick, which were deemed more culturally appropriate (Ganguli et al., 1996). In the learning phase, the list is read out to the participant, who is then asked to recall the words that they remember. This process is repeated three times, giving a total learning score out of 30. Five minutes later the participant is again asked to recall the 10 words, giving a delayed recall score out of 10; additional information for DSM-IV dementia diagnosis and Clinical Dementia Rating (CDR) (Morris, 1993) is obtained from;

(v) an extended informant interview, the modified (Dementia Diagnosis and Subtype) History and Aetiology Schedule (Dewey and Copeland, 2001) providing information on dementia onset and course.

vi) The NEUROEX, a structured neurological assessment of lateralising signs, parkinsonism, ataxia, apraxia and primitive 'release' reflexes (Broe et al., 1998, Broe et al., 1976) .

vii) Behavioural and Psychological Symptoms of Dementia (BPSD) assessed using an informant questionnaire, the Neuropsychiatric Inventory (NPI-Q) (Kaufer et al., 2000).

Participants were allocated to the category of 10/66 dementia when they scored above a cutpoint of predicted probability of dementia estimated from the logistic regression equation developed and validated cross-culturally in the 10/66 international pilot study, using coefficients from the GMS, CSI-D informant and cognitive test interviews and the

modified CERAD 10 word list learning tasks (Prince et al., 2003). DSM-IV dementia is a criterion-based diagnosis requiring impairment in memory and at least one other domain of cognitive function, linked to social or occupational impairment, not better accounted for by delirium or other mental disorder. DSM-IV dementia criteria were applied directly using a computerized algorithm; full details are available in an open access publication (Prince et al., 2008). The second approach involved the direct application of research diagnostic criteria for DSM-IV and for the following dementia subtype diagnoses; NINCDS-ADRDA Alzheimer's disease criteria (McKhann et al., 1984), NINDS-AIREN vascular dementia criteria (Roman et al., 1993), and Lewy Body Dementia (McKeith IG et al., 1996).

2.5.2 Main exposures

2.5.2.1 Sociodemographic variables

- a) Age was formally determined on revisit for interview, using the stated age of the participant, the age recorded on any official documentation, the age according to an informant, and, in the event of unresolved discrepancies, the age according to an event calendar.
- b) Level of education (none/ some, but did not complete primary/ completed primary/ completed secondary/ completed tertiary);
- c) Ethno-racial identity: Participants were classified according to self-report (or that of a family member) on family ancestry, coupled with the interviewer's perception of

ethno-racial identity, using well-established groups used in the Cuban census – ‘Blanco - white’, ‘Mestizo - mixed’ and ‘Negro - black’.

d) Sex, marital status, household living arrangements and availability of children for support, literacy, religion, affiliation and practice, community social activity, social support, social network, were also recorded. Similar demographic information was obtained on informants.

e) Migration status – Residence at birth.

2.5.2.2 Socioeconomic variables

Best occupation (self and spouse), current occupational status. Sources and amount of income; household assets (car, television, refrigerator, telephone, mains water supply, plumbed inside toilet), an assets index was calculated (number of assets in the household categorised: 0–2; 3–5 and 6 or more assets); food insecurity (“do you ever go hungry because there is not enough food to eat?”) are gathered with a standardised questionnaire.

2.5.2.3 Health conditions

a) Physical health is assessed by a standardized questionnaire containing information on self-reported diagnoses (diabetes, stroke, heart disease, high blood pressure) and eleven commonly occurring impairments (Duke University

Centre for the Study of and Human, 1978). Self-reported of chronic non-communicable diseases was based on a standardized questionnaire that included questions such as, “Have you ever been told by a doctor that you had a stroke / heart attack / angina / diabetes?” and a description of episodes.

- b) Self-reported stroke was ascertained with the question “have you ever had a stroke that needed medical attention?” If the answer was “yes” they were asked “what happened?” The answer was coded positive only if the participant or informant gave a clear history of sudden onset of unilateral paralysis and/or loss of speech and/or blindness lasting for at least 24 hours; thus, previous transient ischaemic attacks were excluded. If the history was supportive of stroke they were asked “who diagnosed this stroke?” (no one /primary healthcare worker/ specialist). Stroke was coded only if a clinician had made the diagnosis.
- c) Hypertension: Two methods were used for diagnosis of hypertension: participant’s self-report (“Have you ever been told that you had high blood pressure? When you were first told? Were you started on treatment? Are you still on treatment?”) and/or blood pressure readings that met World Health Organization/ International Society of Hypertension (WHO-ISH) cut-off points (systolic pressure ≥ 140 mm Hg and/or diastolic pressure ≥ 90 mm Hg) (International Society of Hypertension, 2003).
- d) Diabetes: Diagnosed diabetes was defined as a self-reported medical diagnosis of diabetes (answering ‘yes’ to the question “have you ever been told by a doctor that you have diabetes?”). Undiagnosed diabetes was defined as a fasting glucose of > 7 mmol/l, among those not reporting a previous medical diagnosis. Those with a self-reported medical diagnosis of diabetes and a fasting glucose of > 7

mmol/l were considered not controlled, while those below this threshold were considered controlled. 'Total diabetes' comprised those with diagnosed or undiagnosed diabetes. Those with diagnosed diabetes were asked "Do you need a special diet, take tablets, or have insulin injections?" and responses were coded as diet alone, oral hypoglycaemics, insulin, or no treatment.

- e) Obesity: Waist circumference was measured in centimetres using a flexible tape measure. Central obesity was defined (Buter et al., 2008) as a waist circumference of more than 40 inches (101.6 centimetres) in men and of more than 35 inches (88.9 centimetres) in women.
- f) Physical impairments: Self-reported physical impairments (Duke University Centre for the Study of and Human, 1978) was categorized as having none, 1-2 and three or more of 11 limiting physical impairments (arthritis or rheumatism; eyesight problems; hearing difficulty or deafness; persistent cough; breathlessness, difficulty breathing or asthma; high blood pressure; heart trouble or angina; stomach or intestine problems; faints or blackouts; paralysis, weakness or loss of one leg or arm; skin disorders such as pressure sores, leg ulcers or severe burns). Impairments were rated if they interfered with activities 'a little' or 'a lot', as opposed to 'not at all' (Fillenbaum and Smyer, 1981).
- g) Self reported of head injury with loss of consciousness.
- h) Disability and functioning. Activity limitation and participation restriction measured by the WHO-DAS II (Chopra et al., 2004), developed by the WHO as a culture-fair assessment tool for use in cross-cultural comparative epidemiological and health services research. In this study we used the 12-item version (a 36 item version is also available), (Sousa et al., 2009).

2.5.2.4 Lifestyle

Where possible this information was elicited from participants; we used informants only for more severely demented participants. The interviewer provided a reliability rating at the end of both the participant and informant interview, and the interview that was rated as most reliable was selected. If the informant and participant interview were given the same reliability rating, we selected the participant interview. Eliciting this data from informants for all participants might slightly have reduced information bias, but would have increased error and missing data.

- a) Smoking: smoker, ex-smoker, non-smoker, and length of exposure; type of tobacco used (cigarettes, cigars, pipe tobacco, chewing tobacco, snuff); average number of units used per day; age at start of habit and age when the person quit, if habit was interrupted. Pack years were calculated for each individual multiplying the average number of packs per day by duration of consumption (number of years). This was restricted to smoked tobacco and was calculated separately for cigarettes, cigars and pipes.
- b) Alcohol consumption: number of units ingested per week, before and after age 65. To determine hazardous drinking before age 65, a cutoff level was established: 14 units/week for women and 21 units/week for men. The maximum usual consumption per week was recorded in units of alcohol, by type of drink: one glass of beer (250 ml = 2 units), one shot of liquor (22 ml = 2 units), or one glass of wine or sherry (175 ml = 2 units), and one bottle of liquor (1000 ml = 32 units).

2.5.2.5 Mental Health

- a) Depression: Diagnostic criteria for depression. Diagnoses of DSM–IV major depression (American Psychiatric Association, 1994) and ICD–10 depressive episode (World Health Organization, 1992.) were both derived using a computerised algorithm applied to GMS (Copeland et al., 1986). The ICD–10 (World Health Organization, 1992.) divides depressive episodes into mild, moderate and severe. The DSM–IV, but not ICD–10, specifies that symptoms should be severe enough to cause ‘clinically significant distress or impairment’ and excludes a diagnosis of major depression if the symptoms are better accounted for by bereavement. The prevalence of each condition was determined with respect to the past month. Information was obtained from the participant or a reliable informant about: past history of depression and treated diagnosis.
- b) Behavioural and Psychological symptoms of dementia assessed using an informant questionnaire, the Neuropsychiatric Inventory (NPI-Q) (Kaufer et al., 2000).

2.5.2.6. Genetics

- a) Self-reported family history of dementia was ascertained with the question: Have any of his/her close relatives such as parents, brothers or sisters had the problem of serious loss of memory, leading to problems with looking after themselves? We then probed for a history suggestive of dementia and age of onset.

- b) APOE Genotyping: We aimed to collect 10 ml blood samples from all participants, from which DNA was extracted, quantitated, and archived at the National Centre for Medical Genetics in Havana. Apolipoprotein E genotype was determined using HhaI digestion of amplified products. Genotypes were determined masked to knowledge of clinical phenotypes.
- c) Admixture estimation: In a population formed by admixture between two or more founding populations, ancestry informative marker genotype data can be used to estimate the admixture of each individual (the proportion of that individual's genome that has ancestry from each founding population). We aimed to estimate admixture in 600 participants, comprising all dementia cases, and a randomly selected sample of controls. Sixty SNPs were used to estimate individual admixture, chosen from the panel assembled by Dr Mark Shriver at Penn State and Mike Smith at NCI (Smith et al., 2004). With an average 40% information content for ancestry, these 60 SNPs would be sufficient to estimate three-way individual admixture proportions with a standard error of less than 0.1. The ADMIXMAP program (Hoggart et al., 2004) was used to generate posterior means of individual admixture from the ancestry informative marker data. In large samples these posterior means are asymptotically equivalent to maximum likelihood estimates.

2.5.2.7 Blood tests (normal reference values in parentheses).

Biochemical tests; fasting glucose (4.2–6.4 mmol/l) and lipid profile: total cholesterol (3.5–6.2 mmol/l); lipoprotein fractions: high-density lipoprotein, HDL (>0.9 mmol/l); very low density lipoprotein, VLDL (<1.04 mmol/l); triglycerides (<1.86 mmol/l). Commercial reagents were used (Roche, USA). Low-density lipoprotein (LDL) concentrations (<3.4 mmol/l) were calculated using the Friedewald formula.

2.5.2.8 Indicators of care arrangements and caregivers strain:

- a) Dependence was determined by an interviewer assessment, after a series of open ended questions on care arrangements, to a key informant: Who shares the home? What kind of help does the participant need inside and outside of the home? Who, in the family, is available to care? What help do you provide? Do you help to organise care? Is there anyone else in the family who is more involved in helping? What do they do? What about friends and neighbours, what do they do? The interviewer then coded whether the participant required no care, care some of the time, or care much of the time.
- b) Caregiver economic strain: whether the caregiver had cut-back or stopped work to care
- c) Caregiver psychological strain, twenty-two items assess the carer's appraisal of the impact their involvement has on their lives (Zarit et al., 1980, Zarit et al., 1986). For each item burden is quantified from 0 (no burden) to 4 (highest burden).

- d) The Self Reporting Questionnaire 20, a 20 item scale of symptoms of common mental disorder (anxiety, depression and somatisation) (Mari and Williams, 1985), a score of eight or above signifying clinically significant morbidity.

2.5.2.9 Other measures

- a) Anthropometric measures. Skull circumference was measured using a cloth tape-measure encircling the nuchal tuberosity and the brow. Leg length was measured, standing, from the highest point of the iliac crest to the lateral malleolus. All dimensions were measured to the nearest centimeter.
- b) Physical assessments – pulse rate, systolic and diastolic resting blood pressure (average of two, sitting and standing), waist circumference, waist/hip ratio, walking test (5 metres walk, turn and return – timed and paces counted).

2.6 Data Management

All data were collected directly onto laptop computers using computerized questionnaires driven by epidata (version 6.01) software. Conditional skips and interactive checking of data consistency were incorporated to the questionnaires. Data is extracted from epidata into SPSS, and all processing (cleaning, processing of derived variables and running of 10/66, DSMIV dementia and other diagnostic algorithms) is carried out using SPSS batch files. The end result is a cleaned, processed and labelled data set that can be exported into STATA for analysis.

I used the 3.2 version of 10/66 data set for Cuba and Stata software version 10.0 for all analysis.

2.7 Analysis

2.7.1 Prevalence phase

1. Sample characteristics

I first described the response rates for the prevalence and incidence wave interviews, the general characteristics of the prevalence sample, and of the incidence sample. I compared the characteristics (using Chi squared test or t-test as appropriate) of those who were reinterviewed, who died, and who were otherwise lost to follow-up between prevalence and incidence phases

2. Prevalence of dementia

I initially described the prevalence of 10/66 and DSM-IV dementia, and any dementia, by age group and gender with robust 95% confidence intervals, adjusted for household clustering. I then used indirect standardization for age and gender to compare the prevalence of DSM-IV dementia and 10/66 dementia in Cuba with that in Europe using the EURODEM meta-analysis of 12 European studies (Lobo et al., 2000). I applied the age and gender specific prevalences observed in EURODEM to the age- and sex-distribution of the Cuban sample to estimate expected numbers of cases in Cuba, were the age- and gender-specific prevalence to have been the same as in EURODEM. The total observed cases were then divided by the total expected cases, and multiplied by 100 to generate a standardized morbidity ratio (SMR). Mid-point exact 95% confidence intervals were calculated using the OpenEpi online calculator (<http://www.sph.emory.edu/~cdckms/exact-midP-SMR.html>). I have also compared the

crude Cuban prevalence with other 10/66 studies conducted in Latin America (Venezuela, Peru, Mexico and Dominican Republic – all using the same, as my Cuban study) and a recently published meta-analytical review of eight Latin-American studies, and generated SMRs with 95% confidence intervals, using the same indirect standardization procedures as described above.

3. Correlates of prevalent dementia

I tested for cross-sectional associations between both 10/66 dementia and DSM-IV dementia and correlates of possible aetiological significance. I concentrated upon those for which associations were unlikely to have been explained by reverse causality; age, rural or urban birthplace (Jorm et al., 1987), education, family history of dementia, history of head injury with loss of consciousness (Jellinger, 2004, Mortimer et al., 1991), past history of depression (Devanand et al., 1996, Jorm et al., 1991), leg length (Kim et al., 2003, Mak et al., 2006), skull circumference (Schofield et al., 1997) and left handedness (Raiha et al., 1998, Li et al., 1992, de Leon et al., 1986, Seltzer et al., 1984). Crude and mutually adjusted associations were estimated using Poisson regression, generating prevalence ratios with 95% confidence intervals, adjusting for household clustering.

4. APOE genotype and prevalent dementia

I estimated cross-sectional associations between APOE genotype and the prevalence of dementia. Since these analyses required a fasting blood sample (from which DNA was extracted), I first assessed the likely generalisability of my findings, and the possibility of non-response bias, by comparing the characteristics of those who did, and did not

provide a fasting blood sample. I then reported the distribution of APOE genotype and APOE allele frequency by 10/66 Dementia status, estimating the effect of APOE genotype on dementia prevalence using the APOE e3/e3 genotype as the reference category. I also compared the prevalence of dementia between those with zero, one or two e4 alleles, and in those with one or two, compared with no e4 alleles. Effects were tested using Poisson regression to generate prevalence ratios with 95% confidence intervals, adjusted for age, gender and education.

In order to assess whether the effect of APOE genotype on dementia (10/66 Dementia and AD subtype) prevalence was mediated by cardiovascular risk factors, I tested the effect of any APOE e4 allele (versus none) controlling incrementally for a) sociodemographics factors and family history of dementia. and b) individually and separately for cholesterol and triglycerides, diabetes, stroke, hypertension, and smoking.

I next assessed associations between APOE e4 allele carriage and cardiovascular risk factors (hypertension, stroke, diabetes, smoking, serum cholesterol and subfractions, and serum triglyceride), stratified by dementia status, and in the whole sample combined. I tested for the main effect of APOE e4 (using Chi squared test or t-test as appropriate), and for possible interactions (effect modification by dementia status – using general linear models or Poisson regression as appropriate).

Finally, I tested the hypotheses that associations between total cholesterol, cholesterol subfractions and triglyceride and dementia (10/66 Dementia and AD subtype) were modified by APOE genotype (any e4 allele versus none). For each lipid, I constructed a

multivariable model using Poisson regression, testing the main effect of APOE e4, the main effect of the lipid (per mmol/L) and the interaction between APOE e4 and the lipid, all controlling for the potential confounding effects of age, gender, education and family history of dementia. In all I tested for 10 interactions (APOE genotype x five lipid profile measures; total cholesterol, HDL, LDL and VLDL subfractions and triglyceride; for the two dementia outcomes).

5. Impact of dementia

I estimated, using Poisson regression adjusted for household clustering, the independent contributions of 10/66 dementia, DSM-IV major depression, and physical health conditions (self-reported clinician diagnosed stroke and number of physical impairments (Duke University Centre for the Study of and Human, 1978) to needing much care, caregiver psychological morbidity and caregiver needing to cut back or give up on paid work to care. Population attributable prevalence fractions were calculated, estimating the proportion of the prevalence of the outcome that could be avoided if each of these health conditions were eliminated, assuming a causal relationship between the health condition and the outcome, and that the associations are unconfounded. We also formally tested for mediation of the effect of dementia through the severity of Behavioural and Psychological Symptoms of Dementia (BPSD) using a Sobel-Goodman mediation test to test for the degree of mediation (%) and its statistical significance.

2.7.2 Incidence of dementia

1. Incidence wave sample characteristics

I first described in detail the incidence wave resource, in terms of the full baseline sample, the dementia free cohort at baseline, and the characteristics of the dementia free cohort that were reinterviewed.

2. Incidence rates

Person-years at risk for the onset of the relevant dementia outcome (DSM-IV dementia or 10/66 dementia) were calculated as the interval between baseline and follow-up assessment, or the mid-point of this interval for those that were found to have developed dementia. Age-specific incidence (with Poisson standard errors and 95% confidence intervals using the Open Epi online calculator <http://www.sph.emory.edu/~cdckms/exact-rate.html>) was estimated, by sex and by age in 5-year bands by dividing the number of cases by the number of person-years contributed in each age band.

3. Hypothesis testing – the effect of APOE genotype and cardiovascular risk factors on the incidence (and prevalence) of dementia

Since many of the subsequent analyses depended upon the availability of a fasting blood sample, I first compared the characteristics of the at risk dementia-free cohort who did and did not provide a fasting blood sample, using Chi-squared tests or t-tests as appropriate.

I then examined the strength of the association between age, sex, educational level, family history of dementia and APOE genotype and cardiovascular risk factors with the prevalence of dementia (10/66 dementia and DSM-IV dementia) using Poisson regression and with the incidence of dementia (10/66 Dementia and DSM-IV dementia) using Cox regression models (without and with accounting for the competing risk of death). The rationale for this strategy was to assess the potential extent of methodological bias arising from estimating associations with these risk factors

a) from cross-sectional as opposed to cohort studies, which are potentially affected by information bias, prevalence bias (associations with survival with dementia as well as the incidence of dementia) and reverse causality

b) from cohort studies given the competing risk of dementia-free death between baseline and follow-up, an outcome that may also be significantly associated with many of the risk factors under consideration.

I therefore used

i) Poisson regression to estimate the associations in the full cross-sectional sample,

ii) Cox's proportional hazards regression (generating hazard ratios, approximating to incidence rate ratios) in the dementia-free at risk cohort, censoring those who had died at baseline.

iii) Stata's `stcrreg` command to implement a competing-risks regression based on Fine and Gray's proportional subhazards model (Fine and Gray, 1999). This is based on a cumulative incidence function, indicating the probability of failure (dementia onset) before a given time, acknowledging the possibility of a competing event, dementia-free death, and generates subhazard ratios.

Risk factors such as sex (men compared with women), family history of dementia (binary variable), APOE genotype (presence vs absence of an APOE ϵ 4 allele), hypertension, stroke, smoking (ever smoked versus never smoked), hazardous drinking, and diabetes were assessed as binary variables. The effects of age per 5 year band and level of education were assessed as ordinal categorical variables. The effects of total cholesterol, triglycerides, and cholesterol subfractions, and pack years of smoking were assessed as continuously distributed variables. All models were controlled for the effects of age, gender and education.

4. APOE genotype and incident dementia – additional exploratory analyses

Given a considerable attenuation of the effect of APOE genotype upon incident, as compared with prevalent dementia, I carried out a series of further exploratory analyses

- a) testing for a dose response effect across those with zero, one or two ϵ 4 alleles
- b) testing for an interaction by age
- c) comparing ages of onset for incident cases with and without any ϵ 4 alleles
- d) testing for an effect of APOE ϵ 4 on mortality (in the whole baseline sample), and assessing the extent to which any effect was either mediated by or modified by baseline dementia status.

5. Effect modification by APOE genotype

Finally, I replicated the analyses previously conducted using cross-sectional data, to test the hypothesis of an interaction between APOE genotype and lipid profile, but examining associations with incident rather than prevalent 10/66 dementia. The analyses were conducted using proportional subhazards regression and were controlled

for age, sex and education. I took the opportunity to extend the analyses to include tests for interaction between APOE genotype and other cardiovascular risk factors for which there have been previous indications of possible effect modification - stroke, hypertension, smoking history and diabetes.

2.7.3 Interaction between ethno racial identity, admixture, APOE and dementia

1. I first describe the characteristics of the cases (any dementia, n=235) and controls (no dementia, n=350) selected for the genetic admixture nested case-control sub-study with respect to age, gender, education, ethnic group identity (white, mixed or black), family history of dementia, depression, stroke, diabetes, hypertension and smoking. All admixture analyses were weighted back using the probability of selection within each APOE genotype separately for case and control groups.
2. Next I describe the proportions assigned to each ethno-racial identity ('white', 'mixed' and 'black'), and the weighted mean individual admixture proportions (European, African and Native American), and, in the sub-sample, test for an association between them using a weighted one way ANOVA.
3. I next tested for an association between ethno-racial identity and APOE genotype and allele frequencies using a Chi-squared test for trend, and an association between APOE genotype and admixture by making a

weighted comparison of mean admixture across groups with no, one or two APOE e4 alleles.

4. I tested for an association between APOE genotype and any dementia with Chi-squared tests and crude and adjusted prevalence ratios derived from a Poisson working model (adjusted for age, sex and educational level). We next estimated the stratum-specific prevalence ratios for the association between any APOE e4 allele and any dementia in the three ethno-racial identity groups, and fitted a ethno-racial identity by APOE interaction term to the model. We also fitted an African admixture by APOE interaction term to the weighted Poisson model in the case-control sub-sample.
5. I finally assessed the separate and joint effects of ethno-racial identity and admixture on dementia prevalence. In the full sample, we describe the crude prevalence of dementia by ethno-racial identity, and the prevalence of dementia standardised for age, sex and education, and age, sex, education and APOE genotype. Alongside the crude and adjusted prevalence, we also provide prevalence ratios from the analogous Poisson model. In the case-control sub-sample we estimated the main effect of admixture (100% African versus 100% European) on dementia controlling for age, sex, education and APOE genotype. Then, in hierarchical models, we estimated the separate and joint effects of ethno-racial identity and admixture controlling only for APOE genotype, and then the joint effects controlling also for age, sex and education.

To control for population stratification, the adjusted prevalence ratio for any APOE e4 allele was further adjusted for ethno-racial identity, and, in the weighted Poisson model in the case-control sub-sample, for admixture.

2.8 Power and Precision Calculations

Prevalence study

Precision calculations indicated that a sample of 3,000 would allow estimation of a typical dementia prevalence of 4.5% (Lobo et al., 2000) with a precision of $\pm 0.7\%$. Assuming that 25% of the population are exposed (one or more APOE e4 alleles - a typical prevalence from Caucasian populations), and that 4% of the non-exposed have dementia, then the study would have 80% power at 95% confidence of detecting an effect (odds ratio) of 1.6 or greater for the association between APOE e4 and dementia. All analysis were carried out using STATA version 9.2. Numbers of missing values are described for each variable used in the analysis. For the multivariate analyses, only those participants with non-missing data for all independent variables were included.

Incidence Study

The power calculations for the 10/66 incidence phase study were based upon the cohort size for all latin American countries combined. Power within the Cuban cohort alone is therefore somewhat limited. However, as an indication, an at risk cohort of 1,892, with a cumulative incidence proportion of 0.09 would generate 80% power to detect a true HR of 1.6 or greater for an association with hypertension assuming a 75% prevalence at baseline. This power estimation was carried out using Stata 8.2 `ssmenu` command (Barthel FM et al., 2006) for sample size and power calculations in complex studies with failure time outcomes.

Case control study

ADMIXMAP (Hoggart et al., 2004) (<http://homepages.ed.ac.uk/pmcckeigu/admixmap/>) was used to generate posterior means of individual admixture from the ancestry informative. With average 40% information content for ancestry, these 60 SNPs would be sufficient to estimate three-way individual admixture proportions with a standard error of less than 0.1 marker data.

CHAPTER 3 RESULTS

3.1 General Characteristics of the Sample

3.1.1 Baseline sample

Of the 3015 older people enumerated, 2944 interviews were completed (response rate = 97.6 %); 2043 in Havana (97.3%) and 901 in Matanzas (98.4%). Sociodemographic characteristics are summarized in Table 1. The median age was 74 years with an interquartile range of 69 to 79 years; 25.4% of the sample was aged 80 years or older. 64.9% were female and 8.9% were living alone. Levels of education were relatively high, with only 2.6% of illiteracy and 16.9% having achieved tertiary education. Around half of the participants were currently married and a third was widowed. Two thirds of participants had six or more household assets and food insecurity was reported by only 5%. There was a high prevalence of cardiovascular risk factors and chronic non-communicable disease; more than 40% of participants were current smokers, 73.9% of participants had been told that they were hypertensive, and 55.6% met WHO/International Society of Hypertension criteria for hypertension, 18.5% had received a diagnosis of diabetes, and 7.8% reported a stroke diagnosed by a clinician.

3.1.2 Incidence phase

Table 1 provides the main characteristics of the participants in the incidence phase, stratified by follow up status. Of the 2,944 baseline sample participants, 131 from one polyclinic were not followed up because of logistic difficulties; therefore only 2,813 were eligible for the incidence phase. Of these, 2007 (71.3 %) were successfully re-interviewed. There were 608 (20.6%) deaths and 198 (6.7%) were lost to follow-up. There were no substantial differences in the characteristics of those interviewed in the baseline and the subset who were successfully followed up. However there were differences which were statistically significant in gender, age and education between those successfully interviewed at the follow up, those who died and those who were not traced. Those who died were older, and more likely to be women and to have lower education.

Table 1. Baseline characteristics of the sample, stratified by follow up status.

	Baseline sample n=2944	Incidence phase			p Value
		Re- interviewed (n=2007)	Died (n=608)	Lost to follow up (n=198)	
Female (MV=0)	1904(64.9%)	1332 (66.4)	365 (60.0)	139 (70.2)	P= 0.005
Age (MV=7)					
65-69	760(25.8%)	607 (30.3)	59 (9.7%)	49 (24.7)	P<0.0001
70-74	789(26.8%)	578 (28.9)	114 (18.8)	55 (27.8)	
75-79	639(21.7%)	435 (21.7)	137 (22.6)	46 (23.2)	
80+	749(25.4%)	381 (19.0)	297 (48.9)	48 (24.2)	
Lives alone (MV=8)	261(8.9%)	174 (8.7)	53 (8.7)	23 (11.6)	P=0.597
Marital status (MV=8)					P=0.963
Married	1271(43.3%)	903 (45.1)	216 (35.8)	80 (40.4)	P<0.0001
Widowed	928(31.6%)	586 (29.3)	239 (39.6)	71(35.9)	
Separated/ Divorced	462(15.7%)	334 (16.7)	78 (12.9)	36(18.2)	
Never married	275 (9.4%)	180 (9.0)	71 (11.7)	11 (5.6)	
Education (MV=8)					
None	75(2.5%)	42 (2.1)	26 (4.3)	5 (2.5)	P<0.0001
Minimal	655(22.2%)	422 (21.1)	166 (27.5)	31 (15.7)	
Completed primary	979(33.3%)	651 (32.5)	222 (36.8)	64 (32.3)	
Completed secondary	728(24.4%)	540 (27.0)	109 (18.1)	56 (28.3)	
Tertiary	499(16.9%)	348 (17.4)	81 (13.4)	42 (21.2)	P=0.730
Socioeconomic indicators					
Number of Assets					
0-3	78 (2.6)	47 (2.4)	20 (3.3)	10 (5.1)	
4-5	951 (32.6)	630 (31.5)	232 (38.2)	45 (22.7)	
6+	1891 (64.8)	1323 (66.2)	355 (58.5)	143 (72.2)	P=0.084
(MV=8)					
Food insecurity (MV=8)	140 (4.8%)	90 (4.5)	39 (6.5)	8 (4.0)	P=0.218
Life style					
Current smoker (MV=9)	563(42.5%)	369 (40.8)	136 (47.4)	37 (45.7)	P=0.484
Hazardous drinker (MV=17)	105(3.6%)	66 (3.3)	31 (5.1)	6 (3.0)	
CV diseases and risk factors					P= 0.661
Hypertension (MV=4)	2 944 (73.9%)	1488 (74.3)	448 (73.7)	154 (77.8)	
Stroke (MV=6)	230 (7.8%)	113 (5.6)	88 (14.6)	15 (7.6)	
Diabetes (MV=16)	543(18.5%)	354 (17.7)	129 (21.5)	36 (18.2)	

MV= missing values

3.2 Prevalence Correlates and Impact of Dementia in Cuba

3.2.1 Prevalence

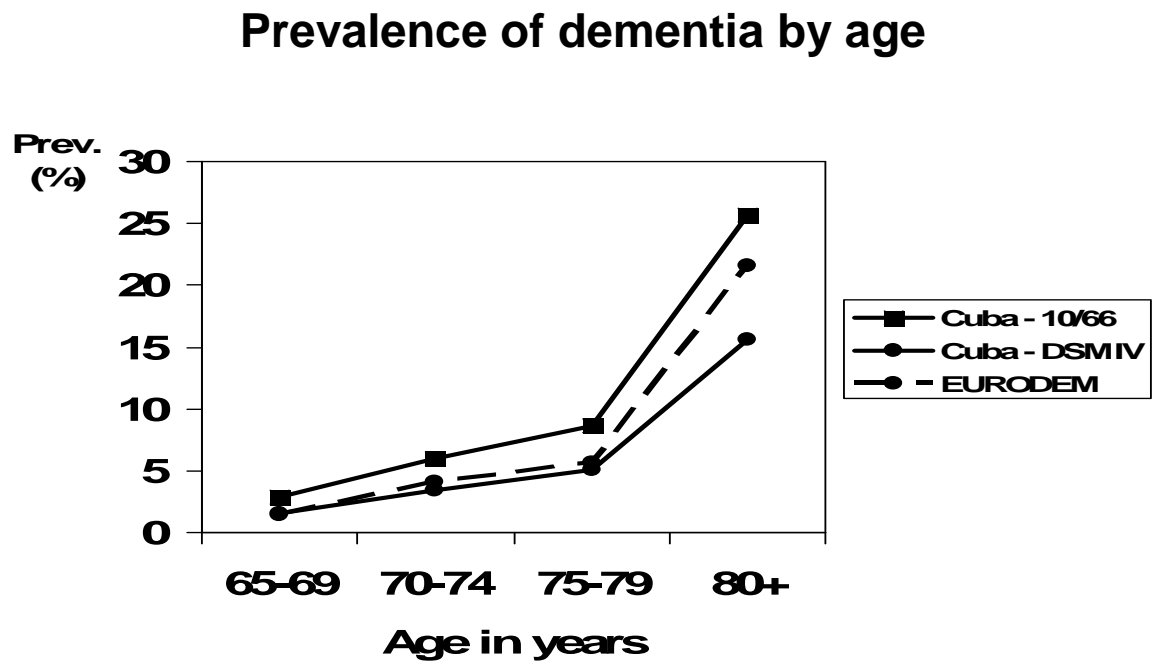
I present in table 2 the prevalence of dementia according to the 10/66 criteria, according to DSM-IV criteria and any dementia (10/66 and/or DSM-IV) by age group and gender. The overall prevalence of 10/66 dementia was 10.8% (95% CI, 9.7%-12.0%) and that of DSM-IV dementia 6.4% (5.6%-7.4%). It can be seen from the data in Table 2 that the prevalence of both 10/66 dementia and DSM-IV dementia increases with age and it is higher in women than in men, particularly among the oldest old. Prevalence was 2.9 % (95% CI 1.7 – 4.1) in the 65–69 age group and 25.7 % (95% CI 22.6 – 28.9) in the ≥ 80 age group. The distribution of dementia cases according to CDR severity was, for 10/66 dementia 22% questionable, 38% mild, 23% moderate and 17% severe, and for DSM-IV dementia 1% questionable, 44% mild, 31% moderate and 24% severe.

The age-specific prevalence of DSM-IV dementia in Cuba is similar but slightly higher than that reported in the EURODEM (Community Concerted Action on the Epidemiology and Prevention of Dementia Group) meta-analysis of European studies (Lobo et al., 2000) (see Figure 2), with an age and gender standardized morbidity ratio of 108.

Table 2. The prevalence (%) of dementia by age group and gender, with 95% confidence intervals derived from robust standard errors, adjusted for household clustering.

Age group		10/66 dementia	DSM-IV dementia	Any dementia
65-69 n=760	Female	2.9 (1.7 - 4.8)	1.9 (1.0 - 3.5)	2.9 (1.4 - 4.4)
	Male	2.9 (1.5 - 5.8)	1.1 (0.4 - 3.3)	2.9 (0.9 - 5.0)
	Total	2.9 (1.9 - 4.3)	1.6 (0.9 - 2.8)	2.9 (1.7 - 4.1)
70-74 n=789	Female	6.1 (4.3 - 8.5)	3.6 (2.3 - 5.7)	6.3 (4.1 - 8.4)
	Male	5.9 (3.7 - 9.3)	3.1 (1.6 - 5.8)	6.2 (3.4 - 8.9)
	Total	6.0 (4.5 - 7.9)	3.4 (2.3 - 4.9)	6.2 (4.5 - 7.9)
75-79 n=639	Female	9.9 (7.3 -13.2)	5.9 (4.0 - 8.6)	9.8 (6.9 - 12.7)
	Male	6.7 (4.1 - 10.8)	4.0 (2.1 - 7.4)	7.04 (3.7 - 10.4)
	Total	8.7 (6.7 - 11.1)	5.1 (3.7 - 7.2)	8.8 (6.6 -11.0)
80+ n= 756	Female	26.8 (23.0 - 30.7)	16.6 (13.3 - 19.8)	26.9 (23.0 - 30.8)
	Male	22.7 (17.3 - 28.1)	13.7 (9.3 - 18.2)	23.2 (17.7 - 28.6)
	Total	25.5 (22.4 - 28.7)	15.7 (13.1 - 18.3)	25.7 (22.6 - 28.9)
All ages n=2944	Female	11.6 (10.3 - 13.1)	7.1 (6.1 - 8.4)	11.8 (10.3 - 13.2)
	Male	9.2 (7.6-11.1)	5.2 (4.0-6.7)	9.3 (7.6 – 11.2)
	Total	10.8 (9.7-12.0)	6.4 (5.6-7.4)	10.9 (9.8 - 12.1)

Figure 2. The prevalence of dementia by age, comparing 10/66 Dementia and DSM-IV dementia in the current study with DSM-IV dementia in the EURODEM meta-analysis



3.2.2 Comparison with other studies of the prevalence of dementia in Latin America

In Table 3 I compare the prevalence of dementia by age group in the Cuban Population found in this study with the previous study conducted in Cuba (EDAP) (Llibre et al., 2009), with a recent meta-analysis of eight studies conducted in six Latin American countries Brazil, Chile, Colombia, Peru, Uruguay , and Cuba (Nitrini et al., 2009) and with the other 10/66 Latin American sites which used the same protocol as mine (Llibre Rodriguez et al., 2008c).

The age-specific prevalence of 10/66 dementia increased from 2.9% between 65 to 69 years aged to 40.6 % for those aged 90 years and over, whereas that of DSM-IV dementia increased from 1.6% to 26.4%. For the 10/66 Latin American studies, including this Cuban study, age-specific prevalence of 10/66 dementia is roughly double that of DSM-IV dementia. Prevalences in Cuba were similar to those found in Dominican Republic for both diagnosis criteria, but higher compared to the other 10/66 Latin American studies in Peru, Mexico and Venezuela. The age specific prevalences found in EDAP a previous study conducted in Havana (Llibre et al., 2009), more or less in the same period of time, are somewhat between the 10/66 and the DSM prevalence of dementia estimated in the present study. The same is true when we compare with the age specific prevalence of the Latin American meta analysis (Nitrini et al., 2009) for which the EDAP study had an important influence.

Table 3. Comparison of crude prevalence of dementia according to age between Cuba 10/66 study, EDAP (Llibre et al., 2009), Latin American 10/66 studies and pooled data of eight studies from six Latin American countries (Nitrini et al., 2009), (%) and 95% CI by age.

Prevalence studies	Age groups (years)							
	Criteria	65-69	70-74	75-79	80-84	85-89	90+	≥ 65
Cuba (n= 2944)	10/66	2.9 (1.7- 4.1)	6.0(4.3-7.6)	8.7 (6.5-10.8)	17.8 (14.2-21.5)	33.0(26.8-39.2)	40.6(31.2-49.9)	10.8(9.7-11.9)
	DSM IV	1.6 (0.7 -2.5)	3.4 (2.2-4.7)	5.2 (3.4-6.9)	10.7 (7.7-13.7)	19.7(14.5-25.0)	26.4(17.8-35.0)	6.4(5.5-7.3)
Cuba EDAP (n=18 351)	DSM IV	3.2 (2.7-3.6)	4.4 (3.7-5.0)	7.00 (6.2-7.8)	12.3(11.0-13.2)	20.3 (17.2-23.4)	30.5(26.9-34.0)	8.2 (7.8- 8.6)
Dominic Republic (n= 2011)	10/66	3.9(2.3-5.6)	6.7(4.6-8.9)	12.6(9.3-15.9)	17.7(13.3-22.1)	23.1(16.8-29.5)	38.9(29.0-48.9)	11.7(10.3-13.1)
	DSM IV	1.3 (0.3-2.3)	3.8 (2.2-5.5)	4.8 (2.7-6.9)	7.5(4.5-10.5)	13.3(8.2-18.4)	18.9(10.9-27.0)	5.4 (4.4-6.4)
Peru Urban (n= 1381)	10/66	2.7(1.0-4.3)	2.6(0.9-4.2)	8.0(4.9-11.1)	13.6(8.3-18.9)	30.5 (21.5-39.6)	48.1(34.4-61.9)	9.3(7.7-11.0)
	DSM IV	1.9(0.5-3.2)	0.8(0.0-1.8)	2.3(0.6-4.1)	5.2(2.0-8.4)	8.2(3.0-13.5)	11.1(2.4-19.8)	3.1(2.2-4.0)
Peru Rural (n= 552)	10/66	3.3(0.7-6.0)	5.7(1.8-9.5)	6.9(1.9-12.0)	10.9(3.7-18.2)	10.5(0.3-20.7)	15.0 (0.0-32.1)	6.5(4.5-8.6)
	DSM IV	0	0	0	2.7 (0.0-6.6)	0	0	0.4(0.0-0.9)
Venezuela (n= 1904)	10/66	2.7 (1.6-3.8)	3.8(2.1-5.6)	6.9(4.2-9.7)	18.2(12.4-24.1)	25.3(16.3-34.3)	38.3(23.9-52.7)	7.1(6.0-8.3)
	DSM IV	1.9(0.5-3.2)	1.1(0.1-2.0)	2.9(1.1-4.7)	8.2(4.1-12.4)	7.7(2.1-13.3)	12.8(2.9-22.7)	0.4(0.0-0.9)
Mexico Urban (n= 1002)	10/66	0.4(0.0-1.2)	4.5(2.3-6.8)	9.7(5.7-13.8)	13.8(7.8-19.9)	25.0(14.9-35.1)	70.6 (46.4-94.7)	8.6(6.8-10.4)
	DSM IV	0.4(0.0-1.2)	2.1(0.6-3.7)	3.4(0.9-5.9)	8.5(3.6-13.3)	10.5(3.5-17.6)	35.3(10.0-60.6)	4.1(2.8-5.3)
Mexico Rural (n= 1000)	10/66	1.3(0.0-2.6)	4.8(2.1-7.4)	8.6(4.9-12.3)	17.9(11.7-24.1)	23.5(13.1-34.0)	53.3(24.7-81.9)	8.5(6.7-10.3)
	DSM IV	1.0(0.0-2.1)	1.2(0.0-2.5)	1.8(0.04-3.6)	4.1 (0.9-7.4)	5.9(0.1-11.6)	13.3(0.0-32.8)	2.2 (1.3-3.1)
Latin American meta analysis (n=31154)	DSM IV	2.4 (2.1- 2.7)	3.6(3.2 -4.0)	7.0(6.4 -7.7)	11.9(10.9- 12.9)	20.2(18.6 -21.8)	33.1(30.0-36.2)	7.1 (6.9-7.4)

* Note that the EDAP study was included in Latin America review

Figures 3 and 4 shows standardised morbidity ratios (SMR) for comparisons (indirect standardisation for age and gender. SMR is a ratio of the observed to expected number of dementia cases. The observed figures come from the Latin American prevalences according 10/66 study samples, the EDAP (Cuba) and Latin American Review, and the expected figures from applying the age-specific and sex-specific prevalence DSM IV and 10/66 (Cuba 10/66 study) to the age and sex distribution of the 10/66 study samples, Cuba EDAP and Latinamerican Review. An SMR of 100 implies that the dementia prevalence in the study sample is similar to that in the reference population, an SMR less than 100 implies that the prevalence in the sample is lower than that in the reference population, and an SMR greater than 100 implies that the prevalence is higher than that in the reference population.

According to DSM-IV criteria, dementia prevalence by age and gender group in Cuba, proved higher than that reported by Dominican Republic SMR 79 (65-94), Puerto Rico 58 (47 – 71) Mexico 67 (49 – 91) and Venezuela 40 (28-54), and lower than that described by the Latin American review with a morbidity standardized ratio by age and sex (SMR) of 113 (108 – 117) and the EDAP in Cuba 123 (117 – 129).

Within the 10/66 Group's prevalence study using the 10/66 Dementia Diagnostic Algorithm, the prevalence of 10/66 Dementia in Cuba was almost similar than that reported for Latin American urban areas., Dominican Republic SMR 102 (90 – 116), Puerto Rico 94 (82 – 106), Peru 92 (77 – 109) and Mexico 87 (70 – 107) and higher than that from Venezuela 69 (57 - 83), EDAP 72 (69 – 77) and Latin American meta analysis with a SMR of 77 (67 – 89).

Figure 3. Standardised morbidity ratios (SMRs) for DSM IV dementia; indirect standardization for age and sex applying the age-specific and sex-specific prevalence (Cuban 10/66 study) from the reference population to the age and sex distribution of the Latin american 10/66 study samples, Cuba (EDAP) and Latin American Review.

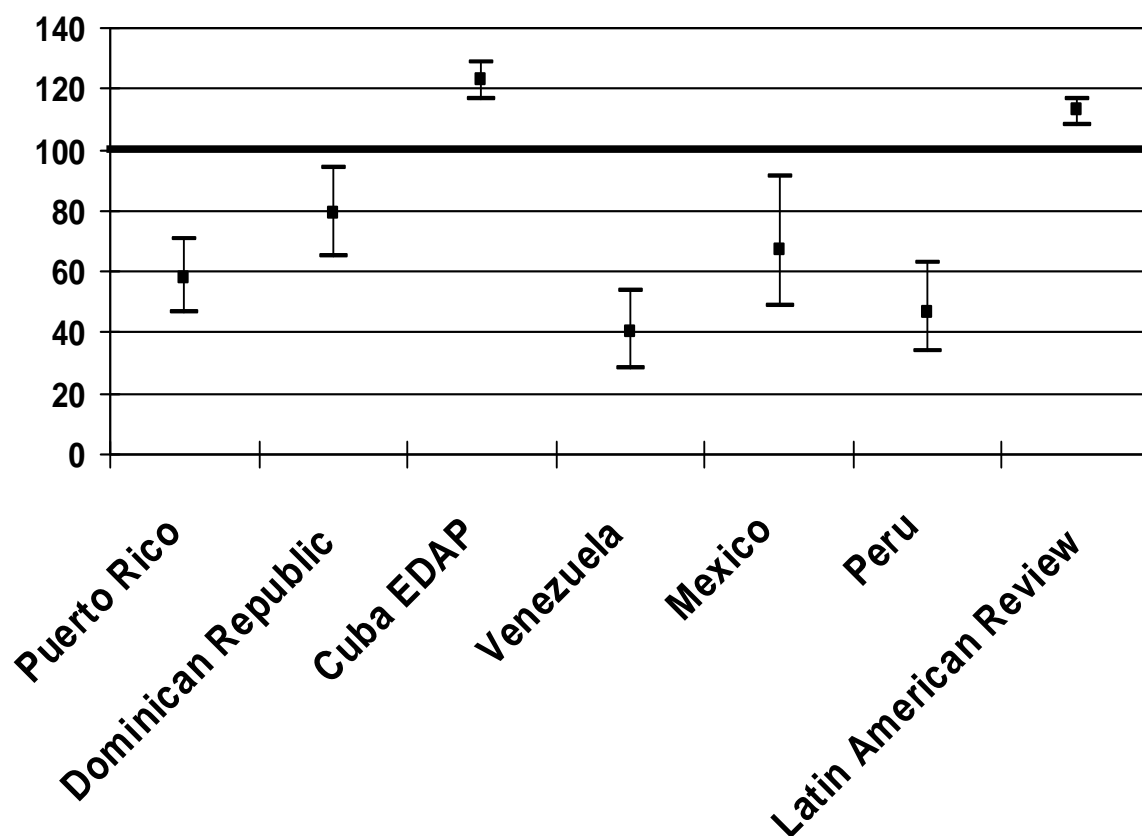
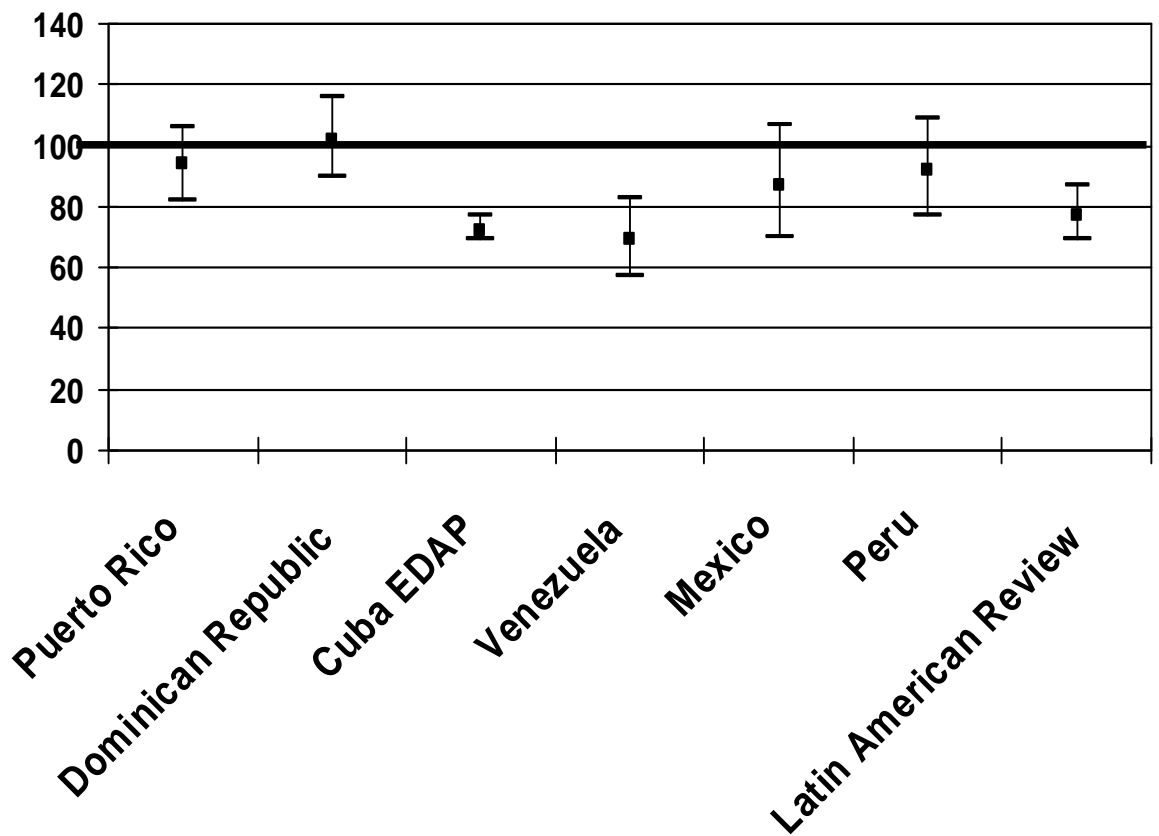


Figure 4. Standardised morbidity ratios (SMRs) for 10/66 dementia; indirect standardization for age and sex applying the age-specific and sex-specific prevalence (Cuban 10/66 study) from the reference population to the age and sex distribution of the Latin american 10/66 studies samples, Cuba (EDAP) and Latin American Review.



3.2.3 Cross sectional correlates of dementia prevalence in Cuba

Associations with dementia were similar for the 10/66 and DSM-IV dementia outcomes. As table 4 shows, for each outcome in the univariate analyses, dementia was associated with increasing age, lower levels of education, shorter leg length and smaller skull circumference, and with a family history of dementia. The crude prevalence ratio of dementia increase with increasing age for both criteria, compared to participants aged 65-69, participants aged 70-74 had two times higher prevalence; for those aged 75-79 compared to those aged 65-69, prevalence of dementia was three times higher and eight times higher for those aged 80 and older. Educational level was inversely associated with the prevalence of dementia. As a sensitivity analysis, we also estimated the effect of leg length in (centimetres) and skull circumference (in centimetres) on dementia prevalence when deployed as linear variables. Dementia prevalence declined with each centimetre increase in leg length (PR 0.98, 95% CI, 0.96–0.99) and with each centimetre increase in skull circumference (PR 0.85, 95% CI 0.80–0.89). There were no associations between dementia and handedness, rural/ urban origins at birth, head injury, or a past history of depression treated by a doctor. 10/66 dementia, but not DSM-IV dementia was associated with female gender.

In the mutually adjusted multivariable models the association between leg length and dementia was no longer apparent. On inspection of the models this was attributable to negative confounding by age and education. The association between female gender and 10/66 dementia was confounded by age and skull circumference.

Table 4: Socio demographic characteristics, and associations with 10/66 dementia and DSM-IV dementia (n=2944)

Exposure	Exposure prevalence (%)	Associations with 10/66 Dementia 10/66 Dementia prevalence (%) in exposed	Crude PR (95% CI)	Multiply adjusted PR ¹ (95% CI) N=2735	Associations with DSM-IV Dementia DSM-IV Dementia prev in exposed	Crude prevalence ratio (95% CI)	Multiply adjusted PR ¹ (95% CI) N=2747
Age	7 mv *						
65-69	760 (25.8%)	2.9 (1.9-4.4)	1 (ref)	1 (ref)	1.6 (0.9-2.8)	1 (ref)	1 (ref)
70-74	789 (26.8%)	6.0 (4.5-7.9)	2.06 (1.25-3.38)	2.09 (1.21-3.61)	3.4 (2.3-4.9)	2.17 (1.11-4.25)	2.22 (1.06-4.65)
75-79	639 (21.7%)	8.6 (6.6-11.0)	2.92 (1.80-4.74)	2.89 (1.68-4.96)	5.1 (3.7-7.2)	3.27 (1.70-6.28)	3.08 (1.48-6.41)
80+	749 (25.4%)	25.7 (22.7-29.0)	8.77 (5.71-13.48)	8.01 (4.90-13.11)	15.6 (13.2-18.4)	9.89 (5.51-17.77)	9.42 (4.88-18.2)
Gender							
Female	1913 (65.0%)	11.7 (10.3-13.2)	1 (ref)	1 (ref)	7.1 (6.1-8.4)	1 (ref)	-
Male	1031 (35.0%)	9.2 (7.6-11.2)	0.79 (0.63-1.00)	1.03 (0.81-1.33)	5.2 (4.0-6.7)	0.90 (0.73-1.12)	-
Education	8 mv						
None	75 (2.6%)	27.0 (18.2-28.2)	1 (ref)	1 (ref)	12.0 (6.3-21.5)	1.00 (ref)	1 (ref)
Minimal	655 (22.3%)	15.9 (13.3-18.9)	0.59 (0.38-0.89)	0.59 (0.37-0.94)	9.9 (7.9-12.5)	0.83 (0.43-1.59)	0.93 (0.44-1.97)
Primary	979 (33.3%)	11.8 (9.9-14.0)	0.44 (0.29-0.66)	0.55 (0.35-0.87)	6.4 (5.1-8.2)	0.54 (0.28-1.04)	0.73 (0.35-1.54)
Secondary	728 (24.8%)	6.5 (4.9-8.5)	0.24 (0.15-0.38)	0.41 (0.25-0.69)	4.4 (3.1-6.1)	0.37 (0.18-0.74)	0.70 (0.32-1.54)
Tertiary	499 (17.0%)	5.8 (4.1-8.3)	0.22 (0.13-0.36)	0.36 (0.20-0.64)	3.8 (2.4-5.9)	0.32 (0.15-0.68)	0.55 (0.23-1.31)
Residence at birth	8 mv						
City	1431 (48.7%)	9.7 (8.3-11.4)	1 (ref)	-	5.5 (4.4-6.8)	1 (ref)	-
Town	715 (24.4%)	11.9 (9.7-14.4)	1.22 (0.95-1.57)	-	7.8 (6.1-10.0)	1.43 (1.04-1.99)	-
Country	790 (26.9%)	11.7 (9.6-14.2)	1.20 (0.93-1.55)	-	7.0 (5.4-9.0)	1.28 (0.91-1.79)	-
Head injury	14 mv						
No	2764 (94.3%)	10.7 (9.6-11.9)	1 (ref)	-	6.5 (5.6-7.5)	1 (ref)	-
Head injury	166 (5.7%)	12.6 (8.3-18.7)	1.18 (0.77-1.80)	-	6.0 (3.3-10.8)	0.93 (0.50-1.73)	-
Handedness	14 mv						
Right handed	2820 (96.2%)	10.7 (9.6-11.9)	1 (ref)	-	6.3 (5.4-7.2)	1 (ref)	-
Left handed	110 (3.8%)	8.3 (4.3-15.1)	0.77 (0.44-1.46)	-	3.6 (1.4-9.3)	0.58 (0.22-1.53)	-
Family history of dementia	10 mv						
No	2385 (81.3%)	9.9 (8.7-11.2)	1 (ref)	1 (ref)	5.6 (4.8-6.6)	1 (ref)	1 (ref)
Yes	549 (18.7%)	14.6 (1.8-17.8)	1.47 (1.16-1.87)	1.60 (1.26-2.03)	9.8 (7.6-12.7)	1.75 (1.29-2.38)	1.73 (1.25-2.40)
Treated depression	10 mv						
No	2537 (86.5%)	11.0 (9.9-12.3)	1 (ref)	-	6.4 (5.5-7.4)	1 (ref)	-
Yes	397 (13.5%)	9.7 (7.1-13.0)	0.88 (0.64-1.21)	-	6.5 (4.5-9.4)	1.02 (0.68-1.51)	-
Anthropometry							
Leg length	127 mv	Case – 83.8 (7.5) ² Non-case – 85.4 (7.4) ²	0.98 (0.96-0.99) ³	1.00 (0.99-1.01) ³	Case – 84.3 (7.8) ² Non-case–85.3 (7.4) ²	0.98 (0.97-1.00) ³	1.01 (0.99-1.03) ³
Skull circumference	57 mv	Case – 55.1 (1.9) ² Non-case – 55.8 (1.9) ²	0.85 (0.80-0.89) ³	0.89 (0.84-0.95) ³	Case – 55.1 (1.9) ² Non-case–55.8 (1.9) ²	0.83 (0.78-0.90) ³	0.89 (0.82-0.97) ³

1. Adjusted for all other covariates in the model; 2. Mean (standard deviation);
3. Change in prevalence per one centimeter increment in the anthropometric index

*mv= missing values

3.2.4 The association between APOE genotype and the prevalence of dementia

3.2.4.1 Availability of data regarding APOE genotype and cardiovascular risk indicators

For the following analyses, of the main effect of APOE genotype on dementia prevalence, and the mediating and/ or effect modifying effects of lipid profile and other cardiovascular risk factors, I used data from those individuals who had agreed to provide a fasting blood sample, from which we extracted DNA to estimate APOE genotype, and which were also analysed for fasting glucose (allowing us to estimate undiagnosed diabetes – fasting glucose ≥ 7.0 mmol/L, lipid profile (triglyceride, total cholesterol and cholesterol sub-fractions). Fasting blood samples were obtained from 2,520 (86.1%) of the 2,944 baseline sample. I carried out analyses to assess the extent of possible non-response bias arising from the unavailability of blood samples from 13.9% of the baseline sample (Table 5). Specifically I tested to see whether sociodemographic variables and major health conditions were differently distributed between those providing and not providing blood samples. Men were possibly slightly under-represented among those not providing blood samples ($p=0.07$). Otherwise, there were no large or statistically significant differences between the two groups regarding age, education, ethnicity, prevalence of dementia, family history of dementia and prevalence of self-reported stroke, diabetes, hypertension and smoking (Table 5) .

Table 5. Baseline characteristics, for the baseline sample, by availability of baseline fasting blood sample.

Variables	Without blood sample N=408	With blood sample N= 2520	P-value
Age in years (mean/ sd)	75.4 (7.2)	75.0 (7.0)	F=2.4, p=0.27
Missing values	0	7	
Male sex (n/ %)	159 (39.0%)	866 (34.4%)	X ² =3.3, 1 df, p=0.07
Education level (n/ %)			
None	12 (2.9%)	63 (2.5%)	X ² =0.27, 1 df, p=0.61
Minimal	96 (23.6%)	554 (22.1%)	
Completed primary	125 (30.7%)	850 (33.8%)	
Completed secondary	111 (27.3%)	615 (24.5%)	
Tertiary	63 (15.5%)	431 (17.2%)	
Missing values	1	7	
Ethno-racial identity			
‘White’	77 (69.4%)	1674 (71.9%)	X ² =1.9, 2 df, p=0.39
‘Mixed’	17 (15.3%)	260 (11.2%)	
‘Black’	17 (15.3%)	395 (17.0%)	
Missing values	97	191	
Dementia (n/ %)	47 (11.5%)	273 (10.8%)	X ² =0.2, 1 df, p=0.68
ICD depressive episode (n/ %)	19 (4.7%)	125 (5.0%)	X ² =0.1, 1 df, p=0.79
Stroke (n/ %)	35 (8.6%)	194 (7.7%)	X ² =0.4, 1 df, p=0.53
Missing values	2	7	
Diabetes (n/ %)	71 (17.5%)	471 (18.8%)	X ² =0.4, 1 df, p=0.53
Missing values	2	14	
Hypertension (n/ %)	295 (72.3%)	1841 (73.1%)	X ² =0.1, 1 df, p=0.75
Smoking (n/ %)	176 (43.2%)	1141 (45.4%)	X ² =0.7, 1 df, p=0.41
Missing values	1	8	
Family history of dementia (n/ %)	75 (18.5%)	473 (18.8%)	X ² =0.0, 1 df, p=0.86
Missing values	2	8	

3.2.4.2 The crude cross-sectional association of APOE genotype with dementia

The distribution of APOE genotype and the APOE allele frequency, by 10/66 dementia status, is shown in table 6. The e2 allele was under-represented, and the e4 allele over-represented among those with dementia. We examined the effect of APOE genotype on dementia prevalence using APOE e3/e3 genotypes as the reference category. After adjusting for age, sex and education, APOE e3/e4 (PR=2.59, 95%CI 2.04-3.28) and APOE e4/e4 genotypes (PR 2.88, 95% CI 1.58-5.27) were strongly associated with dementia. However, there was no apparent protective effect of the e2 allele. The prevalence of dementia was more than double in APOE carriers compared to that in non-carriers (adjusted PR=2.58, 95%CI 2.06-3.22).

Table 6. APOE Genotype and APOE allele frequency by 10/66 dementia status, with crude and adjusted prevalence ratios and 95% confidence intervals

		Dementia N(%) 273	No dementia N(%) 2247	Whole sample N(%) 2520	Crude PR (95% CI)	Adjusted¹ PR (95% CI)
APOE genotype	E2/e3	24 (8.8%)	255(11.4%)	29 (11.1%)	0.97 (0.64-1.46)	0.96 (0.64-1.44)
	E2/e4	2 (0.7%)	15 (0.7%)	17 (0.7%)	1.33 (0.36-4.91)	1.42 (0.37-5.45)
	E3/e3	162 (59.3%)	1663(74.0%)	1825(72.4%)	1.00 (ref.)	1.00 (ref.)
	E3/e4	77 (28.2%)	285 (12.7%)	362 (14.4%)	2.40 (1.88-3.06)	2.59 (2.04-3.28)
	E4/e4	8 (2.9%)	29 (1.3%)	37 (1.5%)	2.44 (1.30-4.57)	2.88 (1.58-5.27)
Number of APOE e4	0	186 (68.1%)	1918(85.4%)	2104(83.5%)	1.00 (ref.)	1.00 (ref.)
	1	79 (28.9%)	300 (13.4 %)	379 (15.0%)	2.36 (1.86-2.99)	2.55 (2.02-3.21)
	2	8 (2.9 %)	29 (1.3%)	37 (1.5%)	2.45 (1.31-4.58)	2.90 (1.59-5.29)
Any APOE allele	1 or 2 e4 alleles	87 (31.9%)	329 (14.6%)	416 (16.5%)	2.37 (1.88-2.98)	2.58 (2.06-3.22)
APOE allele frequency	E2	0.048	0.060	0.059	X ² = 61.7, 1 df, P< 0.001	
	E3	0.778	0.860	0.851		
	E4	0.174	0.080	0.090		

1 Adjusted for age, sex and education

3.2.4.3 Mediation through cardiovascular risk factors

In order to assess if the effect of APOE 4 on dementia is mediated by cardiovascular risk factors I then adjusted for sociodemographics factors and family history of dementia. and then controlling separately cholesterol and triglycerides, diabetes, stroke, hypertension, and smoking alone or with cholesterol and triglycerides. Adjusting, using Poisson regression models, for sociodemographics characteristics (age, gender, education, family history of dementia) lipid profile (cholesterol, triglycerides, LDL, HDL and VLDL) and others vascular risk factors (diabetes, stroke, hypertension , smoking and alcohol) had little effect on the central estimate prevalence ratio for the association between APOE e4 and both 10/66 dementia and AD (Table 7).

Table 7 Crude and adjusted prevalence ratio (PR) (Poisson Regression) for the association between one or more Apoe_4 alleles and dementia and Alzheimer's disease (A.D)

Crude and adjustment	10/66 Dementia		AD	
	PR	(95% CI)	PR	(95% CI)
1 unadjusted	2.37	(1.88 – 2.98)	2.42	(1.78 – 3.28)
2 age, gender and education and family history	2.54	(2.04 – 3.17)	2.59	(1.94 – 3.47)
3 + cholesterol + triglycerides	2.55	(2.03 – 3.21)	2.69	(1.99 – 3.64)
4 + diabetes	2.54	(2.02 – 3.20)	2.75	(2.04 – 3.71)
5 + diabetes + cholesterol + triglycerides	2.53	(2.01 – 3.19)	2.74	(2.03 – 3.70)
6 + Stroke	2.59	(2.07 – 3.24)	2.63	(1.97 – 3.73)
7 + Stroke + cholesterol + triglycerides	2.62	(2.08 – 3.30)	2.74	(2.03 – 3.71)
8 + Hypertension	2.54	(2.04 – 3.17)	2.60	(1.95 – 3.46)
9 +Hypertension + cholesterol + triglycerides	2.56	(2.04 – 3.22)	2.70	(2.01 – 3.65)
10 + Smoking	2.54	(2.03 – 3.17)	2.60	(1.94 - 3.47)
11 + Smoking + cholesterol + triglycerides	2.55	(2.03 – 3.21)	2.70	(2.00 – 3.65)
12 ALL	2.61	(2.10 – 3.29)	2.79	(2.07 – 3.76)

3.2.4.4 Interaction between lipids, APOE genotype and prevalence of dementia

This analysis includes 2,520 participants who gave blood samples for APOE genotyping and lipid profile. Table 8 displays demographics, vascular risk factors and lipid profile in participants according to APOE e4 genotype and dementia status.

Carriage of one or more APOE e4 allele was associated with an increased prevalence of stroke and diabetes, and a higher mean total cholesterol, contributed mainly by the LDL subfraction. There was also a non-significant trend towards a higher prevalence of family history of dementia among carriers (22.7%) than non-carriers (18.1%) ($p=0.07$).

Having stratified these associations according to 10/66 dementia status, it was apparent that there were several statistically significant interactions, with the effect of APOE e4 carriage on the demographic and cardiovascular outcomes modified according to dementia status. Thus, APOE e4 carriers tended to be younger than non-carriers, particularly amongst those with dementia. While the prevalence of stroke was higher among carriers than non-carriers in those free of dementia, the trend was in the opposite direction for 10/66 dementia cases. The mean serum triglyceride level was higher in carriers than non-carriers, but only among those with dementia. Conversely, mean total cholesterol was higher in APOEe4 carriers than non-carriers for dementia non-cases, with no such difference seen among dementia cases; however, this interaction was not statistically significant ($p=0.25$). Family history of dementia was more frequently reported among APOE e4 carriers than non-carriers regardless of dementia status (test for interaction, $p=0.93$).

Table 8 The association between APOE status and various demographic variables, and cardiovascular disease or cardiovascular risk factors, stratified by 10/66 dementia status

Outcome	Whole sample			Stratified by 10/66 dementia case status				Test for APOE x 10/66 Dementia interaction ²
	APOE e4 (n = 278)	No APOE e4 (n=2104)	Test for main effect of APOE ¹	Cases (10/66 Dementia)		Non-cases (10/66 Dementia)		
				APOE e4 (n = 80)	No APOE e4 (n = 172)	APOE e4 (n = 278)	No APOE e4 (n=1 692)	
Mean age, y (SD)	74.6 (6.8)	75.1 (7.0)	2.1, 0.15	79.0 (8.1)	82.0 (7.2)	73.4 (5.8)	74.5 (6.7)	0.04
Female (n, %)	272 (65.4)	1382 (65.7)	0.0, 1.00	62 (77.5)	130 (75.6)	205 (73.7)	1248 (65.2)	0.96
Completed primary education (n, %)	318 (77.4)	1574 (75.1)	0.9, 0.35	51 (60.7)	107 (59.4)	267 (81.9)	1463 (76.6)	0.68
Family history of dementia	94 (22.7)	379 (18.1)	3.4, 0.07	24 (30.0)	43 (25.0)	62 (22.3)	324 (17.0)	0.93
Hypertension	312 (75.1)	1529 (72.7)	1.1, 0.31	61 (76.3)	126 (73.3)	213 (76.6)	140 (73.2)	0.96
Stroke	42 (10.2)	152 (7.2)	3.8, 0.05	13 (16.3)	41 (23.8)	25 (9.0)	115 (6.8)	0.03
Diabetes	108 (29.8)	443 (24.0)	5.3, 0.02	10(12.5)	22 (12.9)	37 (13.3)	222 (13.1)	0.10
Smoking (ever smoked)	186 (45.2)	955 (45.5)	0.0, 0.86	36 (44.7)	68 (39.5)	127 (45.9)	780 (46.1)	0.31
Mean cholesterol (SD)	5.51 (1.2)	5.29 (1.2)	10.3, 0.001	5.35 (1.2)	5.31 (1.0)	5.55 (1.2)	5.29 (1.2)	0.25
Mean HDL (SD)	1.20 (0.4)	1.19 (0.4)	0.07, 0.79	1.13 (0.4)	1.14 (0.4)	1.23 (0.5)	1.19 (0.4)	0.70
Mean LDL (SD)	3.65 (1.3)	3.45 (1.2)	6.4, 0.01	3.52 (1.3)	3.46 (0.9)	3.66 (1.3)	3.48 (1.2)	0.37
Mean (SD) triglycerides	1.62 (0.9)	1.57 (0.9)	1.2, 0.28	1.75 (1.1)	1.43 (0.8)	1.59 (0.9)	1.58 (0.9)	0.03
Mean VLDL (SD)	0.69 (0.4)	0.68 (0.4)	0.5, 0.49	0.71 (0.3)	0.59 (0.3)	0.69 (0.4)	0.68 (0.4)	0.10

1. T-test (F value and p-value) or Chi squared test (Chi square and p-value) as appropriate

2. Test for statistical test for significance of dementia x APOE e4 interaction term, derived from general linear models (continuous outcome) or Poisson regression models (dichotomous outcome) fitting the main effect of dementia, the main effect of APOE and the interaction between them

As described in the background literature review (**section 1.5.3**), other studies had reported inconsistent evidence for interactions between APOE genotype, lipid profile and dementia AD risk. I therefore conducted further multivariable analyses to test for these associations, controlling for the potential confounding effects of age, gender, education and family history of dementia, conducting separate regression analyses for the outcomes of 10/66 dementia and the AD subtype. Table 9 summarises the results of these analyses.

I tested for a total of 10 interactions (APOE genotype x five lipid profile measures; total cholesterol, HDL, LDL and VLDL subfractions and triglyceride; for the two dementia outcomes). Of these just two of the interactions were statistically significant for the 10/66 dementia outcome, and one for AD. There was a particularly large and statistically significant interaction between APOE genotype and VLDL cholesterol subfraction for both 10/66 dementia (PR 2.39, $p=0.01$) and AD (PR 2.16, $p=0.05$) the effect in each case being that VLDL was inversely associated with dementia risk in the absence of an e4 allele (10/66 dementia PR 0.44, 95% CI 0.26-0.74; AD PR 0.85, 95% CI 0.52-1.37), increasing the risk only in the presence of an e4 allele (10/66 PR 1.05; AD PR 1.84), and that the risk effect of APOE e4 was stronger at higher VLDL levels. For the 10/66 dementia outcome, triglyceride was also inversely associated with dementia risk in the absence of an e4 allele (PR 0.80, 95% CI 0.65-0.99), and the risk effect of APOE e4 increased with increasing triglyceride level. There was also a borderline statistically significant interaction, in the same direction, for triglyceride x APOE for the AD outcome ($p=0.06$).

Table 9. Prevalence ratios (PR) and 95% Confidence Interval (CI) for the interactive effects of lipid profile and APOE 4 genotype on dementia and Alzheimer's disease (AD) risk controlling for age, gender, education and family history of dementia .

	10/66 Dementia			Alzheimer's disease		
Model	PR	95% CI	p Value	PR	95% CI	p Value
Total Cholesterol						
Total Cholesterol (per mmol/L)	1.02	0.92 – 1.13	0.77	1.07	0.95 – 1.20	0.27
Genotype (e4 vs no e4)	4.45	1.56 – 12.70	0.005	2.59	1.94 – 3.47	<0.001
Interaction	0.89	0.74 – 1.08	0.24	0.96	0.75 – 1.23	0.75
Triglyceride						
Triglyceride (per mmol/L)	0.80	0.65 – 0.99	0.05	0.95	0.80 – 1.13	0.59
Genotype (e4 vs no e4)	1.43	0.89 – 2.29	0.14	2.71	2.01 – 3.66	<0.001
Interaction	1.40	1.07 – 1.81	0.01	1.34	1.00 – 1.83	0.06
HDL subfraction						
HDL (per mmol/L)	0.79	0.52 – 1.19	0.26	0.90	0.57 – 1.42	0.66
Genotype (e4 vs no e4)	2.62	1.11 – 6.20	0.03	2.55	1.79 – 3.64	<0.001
Interaction	0.94	0.46 – 0.93	0.87	0.65	0.28 – 1.62	0.35
LDL subfraction						
LDL (per mmol/L)	1.00	0.89 – 1.12	0.98	1.02	0.89 – 1.16	0.79
Genotype (e4 vs no e4)	3.36	1.54 – 7.32	0.002	2.52	2.01 – 3.66	<0.001
Interaction	0.91	0.74 – 1.12	0.64	0.94	0.71 – 1.25	0.66
VLDL subfraction						
VLDL (per mmol/L)	0.44	0.26 – 0.74	0.002	0.85	0.52 – 1.37	0.49
Genotype (e4 vs no e4)	1.39	0.83 – 2.33	<0.001	2.55	1.80 – 3.62	<0.001
Interaction	2.39	1.19 – 4.77	0.01	2.16	1.00 – 4.65	0.05

HDL = high-density lipoprotein.

LDL = low-density lipoprotein

VLDL = very low-density lipoprotein

3.2.5 The impact of dementia

In order to assess the impact of dementia compared to that of other chronic disorders, I first compared the distribution of three key indicators of impact; needs of care, caregivers reporting cutting back on work to care and caregiver strain between those with 10/66 dementia, those with physical impairments but no dementia, and others (i.e. free of both dementia and physical impairments) (Table 10). Those with 10/66 dementia diagnosis were more likely to need much care (45.2% of those with dementia, 2.3% of those with physical impairments but no dementia, and 0.8% of others needed much care), to have caregivers needing to cut back on work to care (19.0% of those with dementia, 1.4% of those with physical impairments but no dementia, and 0.4% of others), and to have clinically significant psychological morbidity (22.5% of those with dementia, 9.5% of those with physical impairments but no dementia, and 7.5% of others). I next estimated the independent effects of major chronic health conditions (10/66 dementia, major depression, number of physical impairments and stroke) upon each of the indicators of impact controlling for participant age and gender, and household assets. Those with 10/66 dementia were 17.8 times more likely to need much care, while their caregivers were 13.4 times more likely to have cut back on work to care and 2.1 times more likely to have clinically significant psychological morbidity compared to people without dementia.

The independent effect of dementia on each of these three outcomes was much higher than those of the other chronic conditions (stroke, depression and other physical

impairments. For needing much care the population attributable prevalence fractions were; dementia 64.6%, depression 1.5% and physical health conditions 23.1%. For cutting back work to care; dementia 57.3%, depression 2.3% and physical health conditions 17.5%. For caregiver psychological morbidity; dementia 10.6%, depression 1.2% and physical health conditions 8.6%.

The severity of behavioural and psychological symptoms (assessed on all participants) was independently associated with each of the three outcomes. I conducted a formal test (Sobel-Goodman mediation test) to test formally for the presence and extent of mediator effect through the severity of behavioral and psychological symptoms. The mediation by BPS was most prominent for the effect of dementia on caregiver psychological morbidity (45.9% of the effect mediated through BPS, $p < 0.0001$). The proportion of the effect of dementia on needing much care mediated through BPS was 8.4% ($p < 0.001$). Mediation of the effect of dementia on caregiver cutting back on work to care was minimal and not statistically significant ($p = 0.68$).

Table 10 Associations (prevalence ratios from Poisson regression models) between health conditions and three indicators of impact

Participant health status	Exposure prevalence	Needing much care (MV=348)		Cutting back work to care		Caregiver psychological morbidity (MV=19)	
		Basic model ¹ (n=2574)	Including BPSD (n=2561)	Basic model ¹ (n=2915)	Including BPSD (n=2881)	Basic model ² (n=2766)	Including BPSD (n=2748)
10/66 Dementia (MV=13)	10.8%	17.8 (11.8-27.0)	15.1 (9.7-23.6)	13.4 (7.4-24.5)	10.6 (5.5-20.5)	2.1 (1.6-2.8)	1.5 (1.1-2.0)
Major depression	1.5%	2.0 (1.0-4.2)	1.8 (0.9-3.8)	2.6 (1.0-6.6)	2.4 (1.0-5.9)	1.8 (1.1-2.9)	1.3 (0.8-2.1)
Stroke (MV=9)	7.8%	2.5 (1.8-3.3)	2.4 (1.8-3.2)	1.7 (1.0-2.9)	1.8 (1.1-3.0)	1.3 (0.9-1.7)	1.2 (0.9-1.7)
Physical impairments (MV=6)							
0	43.9%	1	1	1	1	1	1
1-2	46.2%	1.1 (0.9-1.6)	1.1 (0.8-1.5)	1.2 (0.8-1.9)	1.2 (0.7-1.9)	1.2 (0.9-1.5)	1.1 (0.9-1.5)
3 or more	9.9%	1.9 (1.2-2.6)	1.7 (1.2-2.5)	1.4 (0.7-2.5)	1.2 (0.6-2.3)	1.4 (1.0-2.0)	1.2 (0.9-1.8)
BPSD (per one point change in NPI-Q severity) (MV=39)	-	-	1.03 (1.01-1.06)	-	1.05 (1.01-1.09)	-	1.08 (1.06-1.11)

1. mutually adjusted for all health conditions, for participant age and gender and household assets

2. mutually adjusted for all health conditions, for participant age and gender, household assets, carer age, carer marital status, carer gender and carer/ informant coresidence (yes/ no)

MV= missing value

3.3 Incidence of Dementia

3.3.1 Description of the incidence wave resource.

One hundred and thirty one participants from one policlinic ('Gonzalez Coro') were not followed-up by design, owing to practical and logistical impediments. Therefore only 2,813 participants out of the 2,944 interviewed in the baseline were included in the follow-up phase of the project. The general characteristics of the baseline sample, those successfully re-interviewed, those who died and those who were lost to follow-up is described in Section 4.1 (Table 1). In total, 2,517 of 2,813 participants interviewed at baseline and included in the follow-up phase were free of dementia and hence eligible for inclusion in the 'at risk' cohort at baseline. Of these, 449 (17.8%) were found to be deceased and 176 (7.0%) refused to participate or were not traced, and 1892 (75.2%) were successfully traced and re-interviewed at follow-up (Table 11). These participants contributed 8679 person years of follow-up, with an average follow-up period of 4.5 years. The mean age at follow-up was 78.1, two-thirds were female and levels of education were relatively high, but 7.7% of participants reporting illiteracy. The occupational attainment was distributed in a similar proportion between professional, semi-skilled and labourer in persons who were successfully followed up.

Table 11. Description of the 10/66 incidence wave data resource

Baseline sample	No (%)
Total baseline sample (n)	2813
Deceased	608 (21.6%)
Refused	20 (0.7%)
Not traced	178 (6.3%)
Re-interviewed	2007 (71.3%)
Dementia free cohort (n)	2517
Deceased	449 (17.8%)
Refused	17 (0.7%)
Not traced/ uncontactable	159 (6.3%)
Re-interviewed	1892 (75.2%)
Characteristics of dementia-free cohort that were reinterviewed	
Person years of follow-up	8679
Median follow-up in years (25 th -75 th centile)	4.5 (3.9-5.2)
Mean age at follow-up (SD)	78.1 (6.1)
Female sex (%)	1249 (66.0%)
Did not complete primary education (%)	414 (21.9%)
Median assets (25 th -75 th centile)	6 (5-6)
Illiteracy (%)	146 (7.7%)
Occupational attainment	
Professional (%)	581 (32.3%)
Trade (%)	234 (13.0%)
Semi-skilled (%)	547 (30.4%)
Labourer (%)	436 (24.2%)

3.3.2 The incidence of dementia

There were 170 incident cases of 10/66 dementia and 77 meeting criteria for DSM-IV dementia. Just one incident case of DSM-IV dementia did not meet 10/66 dementia criteria. The crude annual incidence rate for 10/66 dementia was 20.5/1000 person years (95% confidence interval 17.6– 23.8) and that for DSM-IV dementia was 9.0 /1000 (95% confidence interval 7.2– 11.3) (Table 12). Incidence tended to be higher in women 21.9/1,000 person-years, (95% CI 18.2–26.2) than men (17.8, 95% CI 13.9–23.5) for 10/66 dementia, but similar according to DSM-IV where incidence was slightly lower in women 9.1 (95 % CI 6.9-12.0) than in men 9.6 (95 % CI 6.6-14.0). Incidence of both dementia outcomes increased exponentially with increasing age. For those aged 80 years and over, annual incidence of 10/66 dementia was 46.7/1000 person years and that of DSM-IV dementia was 16.5 /1000 person years (DSM-IV dementia) (Table 12).

Table 12. Annual incidence rates (per 1000 person years) for DSM IV and 10/66 dementia criteria by sex and age.

Age group	Gender	10/66 dementia		DSM-IV dementia	
		Cases/ pyears	Incidence (95 % CI)*	Cases/ pyears	Incidence (95 % CI)*
65-69 n=587	Female	9/1803	5.0 (2.6 - 9.6)	5/1803	2.7 (1.2 - 6.6)
	Male	7/936	7.5 (3.6 - 15.7)	4/936	4.3 (1.6 - 11.4)
	Total	16/27	5.8 (3.6 - 9.6)	9/275	3.3 (1.7 - 6.3)
70-74 n=545	Female	32/1599	20.0 (14.5 - 28.3)	14/1599	8.8 (5.1 - 14.8)
	Male	12/903	13.3 (3.7 - 9.3)	9/ 903	10.0 (5.2 - 19.2)
	Total	44/250	17.6 (13.1 - 23.6)	23/2558	9.0 (6.0 - 13.4)
75-79 n=405	Female	32/1142	28.0 (19.8 - 39.6)	13/1142	11.4 (6.6 - 19.6)
	Male	15/577	26.0 (15.6 - 43.1)	8/577	13.8 (6.9 - 27.7)
	Total	47/172	27.3 (20.5 - 36.4)	21/178	11.8 (7.7 - 18.1)
80+ n= 309	Female	46/926	49.6 (37.2 - 66.3)	18/995	18.1 (11.4 - 28.7)
	Male	15/379	39.6 (23.9 - 65.6)	5/401	12.4 (5.2 - 29.9)
	Total	61/131	46.7 (36.4 - 60.1)	23/140	16.5 (10.9 - 24.8)
All ages n= 1,886	Female	120/5484	21.9 (18.2 - 26.2)	50/5484	9.1 (6.9 - 12.0)
	Male	50/2807	17.8 (13.5 - 23.5)	27/2807	9.6 (6.6 - 14.0)
	Total	170/8292	20.5 (17.6 - 23.8)	77/8517	9.0 (7.2 - 11.3)

3.4 Cardiovascular and Genetic Risk Factors for Dementia

I examined the strength of the association between age, sex, educational level, family history of dementia and APOE genotype and cardiovascular risk factors with the prevalence of 10/66 dementia using Poisson regression and with the incidence of dementia using Cox regression models (without and with accounting for the competing risk of death).

3.4.1 Blood tests

Fasting blood samples were obtained at baseline from 1 888 (75.0%) of the 2517 dementia-free cohort, and from 1888 (99.7%) of the 1892 of the dementia-free cohort that was subsequently successfully re-interviewed. I tested again to see whether sociodemographic variables and major health conditions were differently distributed between those providing and not providing blood samples in the interviewed incident cohort . Prevalence of dementia was over-represented among those providing blood samples ($p=0.01$). Otherwise, there were no large or statistically significant differences between the two groups regarding age, gender, education, ethnicity, family history of dementia and prevalence of self-reported stroke, diabetes, hypertension and smoking (Table 13).

Table 13. Baseline characteristics, for the dementia incidence cohort, by availability of baseline fasting blood sample.

Variables	Without blood sample N=336 (17.8%)	With blood sample N= 1 552 (82.2%)	P-value
Age in years (mean/ sd)	73.8 (6.1)	73.4 (6.1)	F=2.4, p=0.27
Male sex (n/ %)	120 (35.7)	518 (33.4)	X ² =0, 674 1 df, p=0.4
Education level (n/ %)			
None	3 (0.9)	30 (1.9)	X ² =6.485 , 1 df, p=0.166
Minimal	78 (23.2)	302 (19.5)	
Completed primary	116 (34.5)	494 (31.9)	
Completed secondary	89 (26.5)	437 (28.2)	
Tertiary	50 (14.9)	286 (18.5)	
Missing values		3	
Ethno-racial identity			
‘White’	57 (66.3)	1092 (72.1)	X ² =1.6, 2 df, p=0.455
‘Mixed’	11 (12.8)	175 (11.6)	
‘Black’	18 (20.9)	246 (16.3)	
Missing values	86	39	
Dementia (n/ %)	19 (5.8)	151 (10.0)	X ² =5,72 1 df, p=0.01
ICD depressive episode (n/ %)	18 (5.4)	58 (3.7)	X ² =1,87 1 df, p=0.17
Stroke (n/ %)	16 (4.8)	75 (4.8)	X ² =0.003, 1 df, p=0.9
Missing values			
Diabetes (n/ %)	52 (15.5)	282 (18.2)	X ² =1.445, 1 df, p=0.229
Missing values			
Hypertension (n/ %)	249 (74.1)	1143 (73.6)	X ² =0.03, 1 df, p=0.862
Smoking (n/ %)	160 (47.6)	693 (44.8)	X ² =0.9, 1 df, p=0.341
Missing values			
Family history of dementia (n/ %)	55 (74.4)	287 (18.5)	X ² =0.825, 1 df, p=0.364
Missing values			

3.4.2 Prospective associations of sociodemographic, genetic and cardiovascular risk factors with incident dementia, with and without accounting for competing risk of dementia-free death, compared with those observed cross-sectionally in the baseline data.

I conducted a series of analyses to estimate and compare the strength of associations between potential risk factors for dementia and both 10/66 and DSM-IV dementia

a) cross-sectionally, with the full baseline data set, using Poisson regression working models to generate prevalence ratios

b) prospectively, using the at risk cohort of those free of dementia at baseline, using Cox's proportional hazards regression to generate hazard ratios (HR). Those who died between baseline and follow-up were censored at baseline. Hence 1852 participants were included in this analysis

c) prospectively, using the at risk cohort of those free of dementia at baseline, using a competing risk proportional subhazards regression to generate sub hazard ratios (SHR), accounting for the competing risk of dementia-free death. With an additional 450 dementia-free deaths, 2302 participants were included in this analysis

Risk factors were tested individually, but all models were controlled for the effects of age, sex and education.

Table 14 gives the prevalence ratio (PR), hazard ratio (HR) and competing risk (SHR) estimates for sociodemographic factors (age, sex and education), familial and genetic factors (family history of dementia and APOE genotype), cardiovascular risk factors (smoking, hazardous alcohol use, hypertension, stroke, diabetes and lipid profiles), and other risk factors of interest from the cross-sectional analysis (skull circumference, leg

length and head injury with loss of consciousness). All analyses were controlled for age, sex, and education.

As previously reported, there was a significant association of increasing age (PR=1.99; 1.76-2.26), family history of dementia (PR=1.61; CI 95% 1.28-2.04), stroke (PR=2.32; CI 95% 1.81-2.99) with prevalence of 10/66 dementia. APOE e4 genotype (PR 2.53; CI 95% 2.02-3.17), and hazardous alcohol use before the age of 65 years (PR 1.69; 95% CI 1.18-2.41) were also associated with an increased prevalence of 10/66 dementia. Education level (PR 0.80; CI 95% 0.72–0.89), hypertension (PR 0.73; CI 95% 0.59–0.90), and skull circumference (PR 0.89; CI 95% 0.84–0.95) were inversely associated. Patterns of association with incident 10/66 dementia were somewhat different. The effect of increasing age seemed somewhat attenuated, particularly when the competing risk of death was accounted for in the analysis. The effect of one or two APOE e4 alleles was also attenuated, and only statistically significant when the competing risk of dementia-free death was accounted for (SHR 1.57, 95% CI 1.05-2.37). The effect of stroke was also attenuated and not apparent when accounting for the competing risk of dementia-free death. The inverse associations with education, skull circumference and hypertension were not apparent with respect to incident 10/66 dementia. Smoking, diabetes, lipid profile, leg length and head injury were not associated with either prevalent or incident 10/66 dementia.

Table 14. Prevalence ratio, Hazard ratio and subhazard ratio (competing risk) with 95% confidence intervals for associations between 10/66 dementia and sociodemographic, familial and genetic, and cardiovascular risk factors, adjusted for age, sex and education

Exposures	Prevalence Ratio (95% CI) (n = 2910)	Hazard Ratio 95% CI (n= 1852)	Competing risk - SHR (95% CI) (n = 2302)
Age (per 5 year band)	1.99 (1.76-2.26) MV=15	1.80 (1.56-2.09) MV=9	1.56 (1.35-1.79) MV=11
Sex (Male vs. female)	0.89 (0.72-1.12) MV=15	0.88 (0.62-1.24) MV=9	0.78 (0.55-1.09) MV=11
Education (per level)	0.80 (0.72-0.89) MV=15	0.93 (0.81-1.08) MV=9	0.95 (0.83-1.09) MV=11
Family history of dementia	1.61 (1.28-2.04) MV=18	1.45 (1.00-2.11) MV=10	1.49 (1.04-2.14) MV=14
APOE genotype (any APOE e4 allele vs. none)	2.53 (2.02-3.17) MV=423	1.48 (0.98-2.24) MV=236	1.57 (1.05-2.37) MV=308
Smoking (ever smoked vs never)	0.91 (0.72-1.14) MV=47	0.91 (0.63-1.29) MV=10	0.83 (0.58-1.18) MV=12
Smoking (per pack year)	1.00 (1.00-1.01) MV=55	1.00 (0.99-1.01) MV=26	1.00 (0.99-1.01) MV=33
Hazardous alcohol user before the age of 65	1.69 (1.18-2.41) MV=23	1.57 (0.86-2.85) MV=13	1.37 (0.76-2.48) MV=16
Hypertension (diagnosed, and/ or meets WHO/ ISH criteria	0.73 (0.59-0.90) MV=15	1.13 (0.78-1.64) MV=13	1.10 (0.76-1.60) MV=15
Self-reported stroke	2.32 (1.81-2.99) MV=17	1.98 (1.17-3.34) MV=10	1.50 (0.89-2.53) MV=12
Diabetes (diagnosed, and/ or meets WHO criteria)	1.22 (0.94-1.58) MV=641	0.85 (0.58-1.25) MV=318	0.80 (0.55-1.16) MV=393
Cholesterol (per mmol/l)	1.05 (0.96-1.15) MV=626	1.03 (0.90-1.18) MV=373	1.05 (0.92-1.19) MV=474
Triglycerides (per mmol/l)	1.02 (0.88-1.19) MV=626	1.04 (0.88-1.24) MV=373	1.05 (0.88-1.25) MV=474
HDL (per mmol/l)	0.77 (0.54 - 1.10) MV=1109	0.70 (0.46-1.08) MV=716	0.74 (0.48-1.12) MV=885
Skull circumference	0.89 (0.84-0.95) MV=67	1.04 (0.95-1.12) MV=42	1.04 (0.96-1.13) MV=54
Leg length	0.99 (0.98-1.01) MV=143	1.00 (0.98-1.03) MV=82	1.01 (0.98-1.03) MV=108
Head injury	1.37 (0.90-2.08) MV=22	1.02 (0.50-2.06) MV=13	0.95 (0.47-1.93) MV=18

I then conducted the same set of analyses, using prevalent or incident DSM IV dementia as the outcomes of interest (Table 15). Findings were very similar to those for 10/66 dementia. Prevalent DSM-IV dementia was associated with older age, a family history of dementia (PR 1.79, 95% CI 1.32 – 2.42), APOE 4 genotype (PR 2.73, 95% CI 2.02–3.69) and stroke (PR 2.50, 95% CI 1.80–3.49), and inversely associated with education (PR 0.86, 95% CI 0.75-0.99), skull circumference (PR 0.89, 95% CI 0.82-0.96) and hypertension (PR 0.69, 95% CI 0.52-0.91). The effect of age on incident DSM-IV dementia was less pronounced than that on prevalent DSM-IV dementia, particularly when competing mortality risk was accounted for. There was no association between APOE genotype, or stroke and incident DSM-IV dementia. There was no protective effect of education, skull circumference or hypertension. Smoking, alcohol use, diabetes, lipid profiles, leg length and head injury were not associated with either prevalent or incident DSM-IV dementia.

Table 15. Prevalence ratio, Hazard ratio and subhazard ratio (competing risk) with 95% confidence intervals for associations between DSM-IV dementia and sociodemographic, genetic and cardiovascular risk factors, adjusted for age, sex and education

Exposures	Prevalence Ratio (95% CI) (n = 2923)	Hazard Ratio (95% CI) (n= 1852)	Competing risk - SHR (95% CI) (n = 2302)
Age (per 5 year band)	2.11 (1.79-2.49) MV=11	1.58 (1.29-1.94) MV=9	1.38 (1.13-1.69) MV=11
Sex (Male vs. female)	0.80 (0.59-1.09) MV=15	1.07 (0.66-1.75) MV=9	0.96 (0.59-1.55) MV=11
Education (per level)	0.86 (0.75-0.99) MV=15	1.00 (0.80-1.23) MV=9	1.01 (0.82-1.25) MV=11
Family history of dementia	1.79 (1.32-2.42) MV=18	1.39 (0.80-2.40) MV=10	1.43 (0.83-2.47) MV=14
APOE genotype (any APOE e4 allele vs. none)	2.73 (2.02-3.69) MV=423	1.04 (0.53-2.03) MV=236	1.09 (0.56 -2.11) MV=308
Smoking (ever smoked vs never)	0.88 (0.65-1.21) MV=47	0.62 (0.35-1.09) MV=10	0.58 (0.33-1.01) MV=12
Smoking (per pack year)	1.00 (0.99-1.00) MV=55	1.00 (0.98-1.01) MV=26	1.00 (0.98-1.01) MV=33
Hazardous alcohol user before the age of 65	1.08 (0.59-1.97) MV=23	1.94 (0.90-4.18) MV=13	1.72 (0.80-3.67) MV=16
Hypertension (diagnosed, and/ or meets WHO/ ISH criteria)	0.69 (0.52-0.91) MV=15	0.94 (0.56-1.59) MV=13	0.92 (0.55-1.56) MV=15
Self-reported stroke	2.50 (1.80-3.49) MV=17	1.45 (0.62-3.39) MV=10	1.14 (0.49-2.67) MV=12
Diabetes (diagnosed,, and/ or meets WHO criteria)	1.19 (0.85-1.66) MV=641	0.72 (0.39-1.33) MV=318	0.67 (0.37-1.23) MV=393
Cholesterol (per mmol/l)	1.05 (0.93-1.18) MV=626	0.98 (0.80-1.19) MV=373	0.99 (0.82-1.21) MV=474
Triglycerides (per mmol/l)	0.92 (0.76-1.11) MV=626	1.03 (0.78-1.34) MV=373	1.04 (0.80-1.36) MV=474
HDL (per mmol/l)	0.80 (0.53-1.20) MV=1109	0.89 (0.49-1.60) MV=716	0.92 (0.51-1.66) MV=885
Skull circumference	0.89 (0.82-0.96) MV=67	1.06 (0.94-1.20) MV=42	1.06 (0.94-1.19) MV=54
Leg length	1.00 (0.98-1.02) MV=144	1.01 (0.98-1.05) MV=82	1.01 (0.98-1.05) MV=108
Head injury	1.11 (0.60-2.05) MV=22	0.76 (0.25-2.38) MV=13	0.73 (0.23-2.27) MV=18

3.4.3 Further explorations of the association of APOE genotype with incident dementia

Given the much attenuated associations of APOE e4 with incident dementia, I decided to explore these associations further using the 10/66 dementia outcome.

I first assessed in more detail the pattern of associations of APOE genotype with incident 10/66 dementia, using competing risks proportional subhazards regression, controlling for age, sex and education. There was no evidence for a dose response effect. Relative to those with no APOE e4 alleles the SHR for those with one was 1.61 (95% CI 1.05-2.45), and the SHR for those with two e4 alleles was 1.24 (95% CI 0.29-5.30). There were, however, only 25 persons in the at risk cohort who were e4/e4, and 255 who had one e4 allele

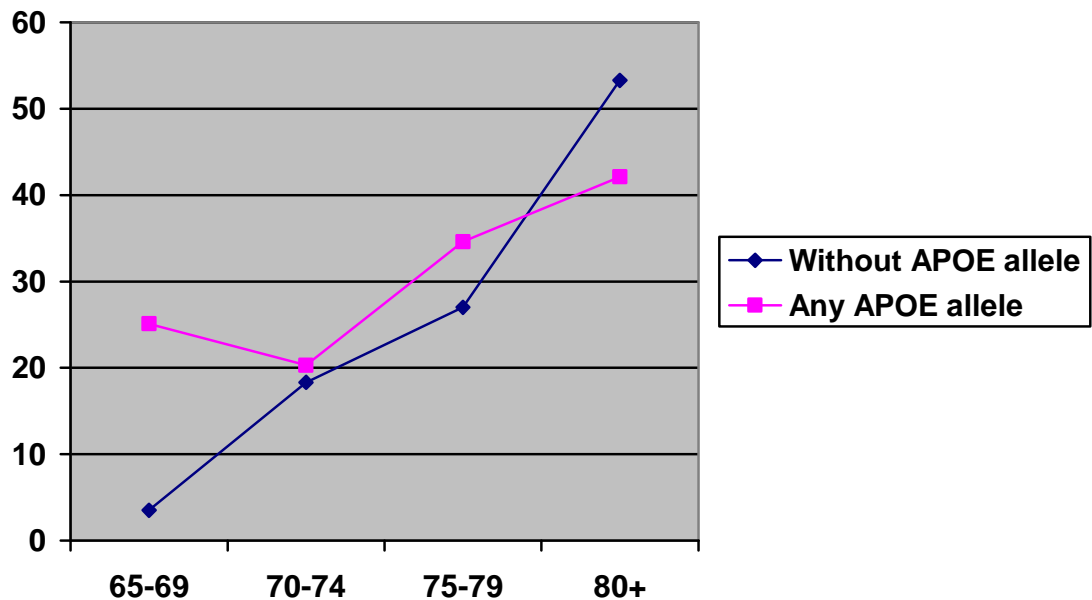
I next explored the effect of age on the association of APOE genotype with incident 10/66 dementia. Table 16 compares the incidence rates of 10/66 dementia according to age group and APOE status. Incidence increases sharply with age for those with no APOE e4 allele, but much less steeply for those with one or two APOE e4 alleles. The effect of APOE genotype on dementia incidence appeared to be principally confined to the youngest age group. For participants aged 65–69 years with one or two APOE e4 alleles, incidence rates for dementia were seven times higher than those participants without APOE allele. Among those aged 80 years and over, dementia incidence was actually lower among APOE e4 carriers than among non-carriers. The pattern is illustrated graphically in Figure 5

The interaction of age with APOE genotype in the association with incident 10/66 dementia was confirmed in a model testing for the main effect of APOE genotype (any e4 allele vs. none), the main effect of age (linear effect per five year increment), and the interaction between the two, controlling also for sex and educational level. The interaction term was statistically significant (SHR 0.71, 95% CI 0.53-0.96), indicating a substantial progressive reduction in the effect of APOE e4 with increasing age, from that estimated for the baseline age group (SHR 3.99, 95% CI 1.71-9.31). Likewise, the estimated effect of age for those lacking an APOE e4 allele (SHR 1.47, 95% CI 1.31-1.64) is reduced in the presence of an e4 allele to a SHR of 1.04.

Table 16. Incidence rates of dementia (per 1000) by age group and APOE status

Age group	Any APOE 4 allele	Without APOE4 allele
65 – 69	25.1 (13.1 – 48.5)	3.5 (1.6 – 7.3)
70 – 74	20.3 (9.7 – 42.6)	18.3 (13.1 – 25.5)
75 – 79	34.6 (16.5 – 72.6)	27.0 (19.5 – 37.5)
80 or more	42.1 (18.9 – 93.8)	53.3 (40.6 – 70.0)
Whole sample	27.7 (19.2 – 39.8)	21.1 (17.7 – 25.0)

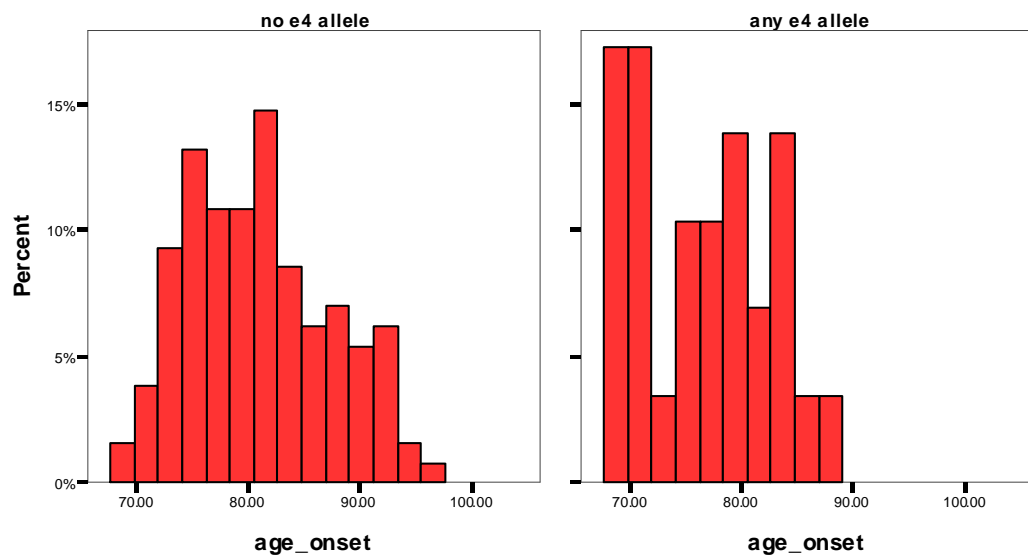
Figure 5. Age and the incidence of dementia for persons with Apolipoprotein E4 compared with persons without an Apolipoprotein E4 allele.



The clear implication of this pattern of incidence with age, is that the age of onset of incident 10/66 dementia cases is younger among those with one or more APOE e4 alleles, compared with those lacking an e4 allele. Histograms illustrating the distribution of ages of onset are provided in Figure 6 below.

Figure 6

Frequency histograms (%) showing the distribution of age of onset of 10/66 dementia for those with and without APOE e4 alleles



The distribution is clearly strikingly different, with that for APOE e4 carriers skewed towards younger ages. The mean age of onset for those with an APOE e4 allele was 76.5 years, and that for those with no e4 alleles is 81.0 years (mean difference 4.6 years, 95% CI 2.0 to 7.1 years, $p=0.001$).

Finally, given that discrepancies between associations of APOE genotype with prevalent and incident dementia might be accounted for by differential mortality, I conducted survival analyses (Cox's proportional hazards analysis) to assess the effect of APOE genotype on mortality in the whole sample, and separately among those with and without 10/66 dementia at baseline. The crude effect of any APOE e4 allele vs. none was HR 1.03 (95% CI 0.83-1.31). After controlling for age, sex and education this increased slightly to 1.09 (95% CI 0.86-1.38). Controlling additionally for baseline 10/66 dementia, the hazard ratio for APOE e4 was 0.94 (95% CI 0.74-1.20). I then extended this model to test for an APOE e4 by 10/66 dementia interaction, which was not statistically significant, although the trend was towards a greater mortality risk associated with APOE e4 for those with dementia (interaction term HR 1.34, 95% CI 0.81-2.20).

3.4.4 Cardiovascular risk factors, APOE genotype and incidence of dementia.

Finally, I replicated the analyses previously conducted using cross-sectional data, to test the hypothesis of an interaction between APOE genotype and lipid profile, but examining associations with incident rather than prevalent 10/66 dementia. The analyses were conducted using proportional subhazards regression and were controlled for age, sex and education. I took the opportunity to extend the analyses to include tests for interaction between APOE genotype and other cardiovascular risk factors for which there have been previous indications of possible effect modification - stroke, hypertension, smoking history and diabetes.

Results of these analyses are summarised in Table 17. None of the cardiovascular risk factor by APOE genotype interaction terms reached statistical significance. Neither was there any consistent pattern or trend in the interaction effects observed across cardiovascular risk factors. However, consistent with the cross-sectional analyses (p 119) there was a trend for the effect of APOE e4 to increase with the levels of VLDL cholesterol and triglyceride, and for higher levels of these lipids to confer risk for 10/66 dementia in the presence of an APOE e4 allele.

Table 17. Proportional subhazards regression (generating subhazard ratios and 95% confidence intervals) testing for the interaction between cardiovascular risk factors and APOE genotype for the incidence of 10/66 dementia, adjusted for age, sex and education

Cardiovascular Risk Factor	Numbers of participants included in the model	Effect of risk factor among those with no APOE e4 alleles	Effect of APOE e4 at baseline of risk factor	Interaction term
Self-reported stroke	1994	1.61 (0.89-2.91)	1.58 (1.03-2.44)	0.90 (0.22-3.68)
Hypertension (diagnosed and undiagnosed)	1990	1.11 (0.73-1.68)	1.25 (0.47-3.32)	1.33 (0.45-3.94)
Smoking (ever vs. never)	1993	0.89 (0.60-1.32)	1.97 (1.21-3.21)	0.52 (0.21-1.26)
Diabetes (diagnosed and undiagnosed)	1791	0.72 (0.47-1.12)	1.33 (0.79-2.24)	1.71 (0.66-4.43)
Total cholesterol (per mmol/L)	1754	1.01 (0.88-1.16)	0.77 (0.07-8.03)	1.12 (0.75-1.68)
HDL cholesterol (per mmol/L)	1383	0.66 (0.40-1.08)	0.68 (0.21-2.20)	1.79 (0.78-4.20)
VLDL cholesterol (per mmol/L)	1440	0.69 (0.39-1.20)	0.77 (0.27-2.16)	2.37 (0.68-8.28)
Triglyceride (per mmol/L)	1754	1.00 (0.82-1.22)	0.97 (0.39-2.41)	1.31 (0.83-2.07)

3.5 Ethnic Identity, Individual Admixture, Apoe Genotype and Dementia

My objectives for this analysis were

1. to analyse the association between ethnic group identity and individual admixture
2. to assess the association of each with APOE genotype
3. to control for the possible effects of population stratification, by estimating the association of APOE genotype with dementia, controlling for ethnic identity and admixture.
4. to test the hypotheses that
 - a. the effect of APOE genotype on dementia is modified by ethnic group, and/ or admixture, with weaker associations among those with ‘mixed’ and ‘black’ ethnic identity and with higher proportions of African admixture
 - b. the prevalence of dementia is lower among those with ‘mixed’ and ‘black’ ethnic identity, and is inversely linearly related to African admixture

For the purposes of this component of my study, I used

- a) Data on participants’ ethnic identity rated by the research workers when blood samples were taken. Of the 2520 participants who had given blood samples, data on both ethnic identity and APOE genotype was available on 2329 (92.4%).
- b) Data on individual admixture estimated from 60 SNPs, informative regarding ancestry. Given the relatively high costs of genotyping 60 SNPs for each participant, I used a nested case control design, selecting all 235 participants with ‘any dementia’ (cases, 231 meeting criteria for 10/66 dementia, 137 meeting DSM-IV dementia criteria,

and 133 meeting both sets of criteria) and a random selection of 349 non-cases (controls, meeting neither set of dementia criteria). For all subsequent case-control analyses, sample weights were used to weight back for the inverse of the probability of selection between case and control groups, and within case and control groups by APOE genotype. For the cases the weights were APOE e2/e3 1.00; e2/e4 1.00; e3/e3 1.11; e3/e4 1.68; e4/e4 1.14. For the controls, these were APOE e2/e3 5.10; e2/e4 3.50; e3/e3 8.16; e3/e4 4.54; e4/e4 2.15.

Table 18 describes the general characteristics of those included in the case control study. Differences between the two groups mainly reflect those noted for the whole sample (see p 99). Cases were older, and more likely to belong to the two lowest educational levels (39.5%), than controls (18.0%). The prevalence of stroke was four times higher in cases than in controls. Ethnic identity was similarly distributed between cases and controls, as were sex, depression, and other cardiovascular risk factors; smoking, hypertension and diabetes.

Table 18. Characteristics of the case control study samples.

Variables	Cases N=235	Controls N=350	Test for difference in means or proportions
Mean age in years (sd)	81.3 (0.50)	73.9 (0.37)	T=12.2, 582df
Missing values	1	0	p<0.001
Male sex (n/ %)	61 (27.1)	118 (34.6)	$\chi^2=3.1$
Missing values	2	1	p=0.08
Education level (n/ %)			$\chi^2=55.2$, 1df
None	13 (5.5)	6 (1.7)	p<0.001
Minimal	80 (34.0)	57 (16.3)	
Completed primary	83 (35.3)	101 (28.9)	
Completed secondary	36 (15.3)	105 (30.0)	
Tertiary	20 (8.5)	81 (23.1)	
Missing values	3	0	
Ethnic identity			$\chi^2=0.6$, 2df
‘White’	147 (70.3)	216 (68.4)	p=0.76
‘Mixed’	22 (10.5)	40 (12.7)	
‘Black’	40 (19.1)	60 (19.0)	
Missing values	26	33	
ICD-10 depressive episode (n/ %)	18 (7.7)	18 (5.1)	$\chi^2=1.1$, 1df
Missing values	0	0	p=0.29
Stroke (self-reported) (n/ %)	48 (20.7)	17 (4.9)	$\chi^2=33.7$, 1df
Missing values	3	0	p<0.001
Diabetes (diagnosed or undiagnosed) (n/ %)	58 (25.1)	90 (25.7)	$\chi^2=0.0$, 1df
Missing values	4	0	p=0.95
Hypertension (diagnosed or undiagnosed) (n/ %)	164 (70.1)	255 (72.9)	$\chi^2=0.4$, 1df
Missing values	1	0	p=0.53
Smoking (ever smoked) (n/ %)	94 (40.3)	154 (44.0)	$\chi^2=0.6$, 1df
Missing values	2	0	p=0.43
Family history of dementia (n/ %)	62 (26.7)	59 (16.9)	$\chi^2=7.7$, 1df
Missing values	3	0	p=0.006

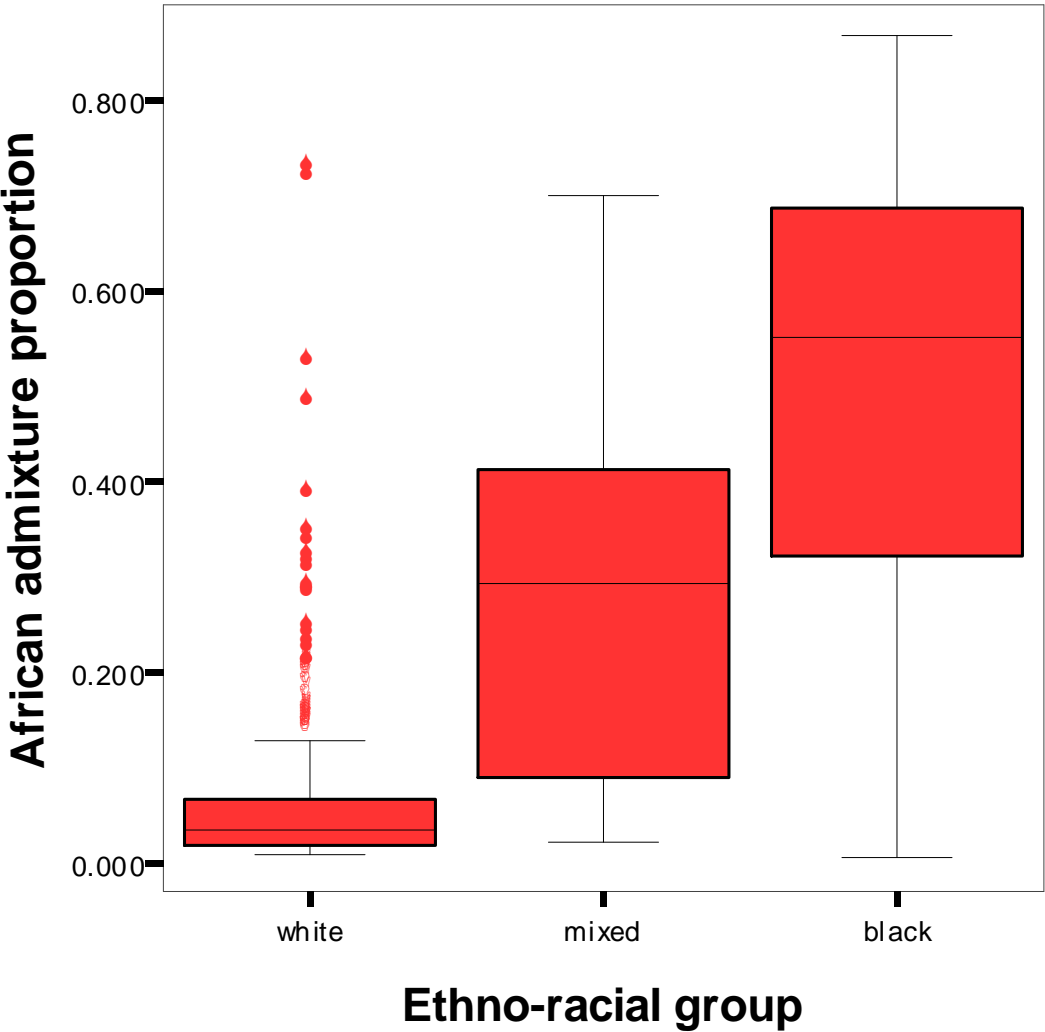
3.5.1 Ethnic identity and individual admixture

As can be seen from table 19 according to interviewer perceptions, 1674 (72%) participants were considered to be ‘white’, while 395 (17%) were considered ‘black’ and 260 (11%) ‘mixed’. There was no association between ethnic identity and either age or sex. However, there was a graded association between ethnic identity and level of education, with those considered ‘white’ having the highest and those considered ‘black’ having the least education. The distribution of Ethnic identity in the sample broadly corresponded to the individual admixture proportions aggregated across the case-control sample. For the case-control sub-sample (n=584) (after weighting back to account for the different sampling fractions for cases and control, and for APOE genotype within case and control groups), the mean individual admixture proportions were; European 81.2% (79.1-83.3%), African 16.2% (14.1-18.3%), and Native American 2.6% (2.3-3.0%). Stratification by ethnic identity (Box-plot in Figure 6) indicated a reassuringly strong association between ethnic identity and individual admixture proportions, but also significant discrepancies. All three groups were substantially admixed with considerable overlap between the three ethnic identities, pure African or European ancestry being the exception. The mean African admixture proportion for the three ethnic groups was 5.8% for ‘white’, 28.6% for ‘mixed’ and 49.6% for ‘black’. A small proportion of those defined as ‘white’ had marked African ancestry and most of those defined as ‘black’ had inherited much of their genome from European ancestors.

Table 19. Distribution of sociodemographic characteristics by ethnic identity

Ethnic identity	‘White’ N= 1674	‘Mixed’ N= 260	‘Black’ N= 395	P value X²
Age (mean/ SD)	75.0 (7.0)	75.7 (7.7)	74.7 (6.9)	F=1.7, P=0.19
Male sex (n/ %)	579 (34.6%)	95 (36.5%)	118 (29.9%)	X ² = 4.0, 2df, P=0.14
Education level (n/ %)				
None	37 (2.2%)	7 (2.7%)	14 (3.6%)	X ² = 25.6,
Some	344 (20.6%)	55 (21.2%)	112 (28.5%)	1 df, P<0.001
Primary	543 (32.5%)	87 (33.5%)	148 (37.7%)	
Secondary	429 (25.7%)	62 (23.8%)	73 (18.6%)	
Tertiary	317 (19.0%)	49 (18.8%)	46 (11.7%)	

Figure 6. Box plot of African admixture distribution by Ethnic identity (weighted)



3.5.2 Ethnic identity and APOE genotype

There was a strong statistically significant graded association between Ethnic identity and APOE genotype, with lower e3 frequency and higher e2 and e4 frequencies moving from ‘white’ to ‘mixed’ to ‘black’ groups (Table 20). According to Ethnic identity, 24.6% of black participants, 14.6% of ‘mixed’ participants, and 15.0% of ‘white’ participants had at least one APOE e4 allele.

Table 20 Distribution of sociodemographic characteristics, APOE genotype and APOE allele frequency by ethnic identity

Ethnic identity	‘White’ N= 1674	‘Mixed’ N= 260	‘Black’ N= 395	P value X²
APOE Genotype (n/ %)				
No e4 allele	1423 (85.0%)	222 (85.4%)	298 (75.4%)	X²= 31.4, 1 df, P < 0.001
Heterozygous (One e4 allele)	241 (14.4%)	32 (12.3%)	77 (19.5%)	
Homozygous (Two e4 alleles)	10 (0.6%)	6 (2.3%)	20 (5.1%)	
APOE allele frequency				
E2	0.058	0.063	0.072	X²= 42.6, 4 df, P = <0.001
E3	0.864	0.852	0.780	
E4	0.078	0.085	0.148	

3.5.3 Admixture and APOE genotype

In the case-control sub-sample, there were also graded associations (after weighting back) between individual admixture and APOE genotype, both with respect to the proportion of African ancestry (higher in those with more e4 alleles) and European ancestry (lower in those with more e4 alleles (Table 21). Native American ancestry was not significantly associated with APOE genotype.

Table 21 Mean admixture proportions by APOE e4 allele status (weighted analysis)

APOE genotype	No e4 allele N= 445	Heterozygous (one e4 allele) N=119	Homozygous (two e4 alleles) N=20	ANOVA for difference between means F (2, 581), P value
Admixture proportions				
African	0.15	0.19	0.35	4.63, p= 0.01
Mean (95 % CI)	(0.13-0.18)	(0.15- 0.23)	(0.22-0.48)	
European	0.82	0.78	0.62	4.99, p=0.007
Mean (95% CI)	(0.80-0.84)	(0.74-0.83)	(0.48-0.75)	
Native	0.03	0.03	0.03	0.43, p=0.65
American	(0.02-0.03)	(0.02-0.04)	(0.02-0.05)	
Mean, (95% CI)				

3.5.4 Does population stratification account for the association between APOE genotype and dementia?

In the full sample, the prevalence of ‘any dementia’ was more than double in APOE carriers compared to that in non-carriers (adjusted PR=2.58, 95%CI 2.06-3.22). This adjusted prevalence ratio was little changed after adjusting also for ethnic identity (PR 2.47, 95% CI 1.96 to 3.12). After weighting back, the association between any APOE e4 allele and dementia, adjusted for age, sex and educational level was naturally similar in the case-control sub-sample, although estimated with less precision (PR 2.54, 95% CI 1.85-3.47). This association was also essentially unchanged after further adjusting for individual admixture (PR 2.57, 95% CI 1.89-3.49).

3.5.5 Is the effect of APOE genotype modified by ethnic identity/ admixture?

Stratifying by ethnic identity in the full sample, the association between any APOE e4 and dementia was similar in ‘white’ (PR 2.83, 95% CI 2.18-3.68) and ‘black’ participants (PR 2.38, 95% CI 1.43–3.95), with no association apparent among those rated as having ‘mixed’ race (PR 0.87, 95% CI 0.25–2.98). However, the likelihood ratio test for the interaction term was not statistically significant ($X^2=4.42$, degrees of freedom=2, $p=0.11$). In a sensitivity analysis, after merging the ‘mixed’ and ‘black’ groups, the interaction between APOE e4 and ethnic identity showed a non-significant trend towards a weaker APOEe4 dementia association among non-whites compared with whites (PR 0.74, 95% CI 0.45-1.24). In the case-control subsample, extending the model to include an APOE by African ancestry interaction term suggested that the effect (prevalence ratio) of any APOE e4 allele would vary continuously from PR 2.93 (95%

CI 1.99-4.31) in those with 100% European ancestry to 1.52 in those with pure African ancestry. However, the interaction term again failed to reach statistical significance (PR 0.52, 95% CI 0.13-2.08), $p=0.36$.

3.5.6 The association between ethnic identity/ admixture and dementia

There were no statistically significant effects of ethnic identity on dementia prevalence, either before or after adjusting for compositional differences (Table 22). The prevalence of dementia was slightly higher among ‘black’ participants and slightly lower among ‘mixed’ participants when compared with ‘white’ participants, these tendencies being amplified after standardizing or adjusting for age, sex and education. After further standardizing or adjusting for the compositional differences in APOE genotype, dementia prevalence among both ‘black’ and ‘mixed’ groups was slightly lower than among those identified as ‘white’.

In the case-control subsample the prevalence ratio for 100% African versus 100% European ancestry was PR 0.81 (95% CI 0.41-0.63). After fitting the APOE x African admixture interaction term, the effect of African ancestry was estimated as PR 1.01 (95% CI 0.43-2.39) in those without an APOE e4 allele and 0.52 in those with an APOE e4 allele – albeit that as noted before the interaction term was not statistically significant.

Table 22. Crude and adjusted dementia prevalence by ethnic identity, with prevalence ratios

		‘White’ N= 1677	‘Mixed’ N= 261	‘Black’ N= 394
Crude prevalence	Any dementia -	190/1751	25/277	49/ 412
	crude prevalence	10.9%	9.0%	11.9%
	(%)	(9.4-12.3%)	(5.5-12.5%)	(8.8-15.0%)
	Crude prevalence ratio	1 (ref)	0.83 (0.55-1.25)	1.10 (0.82-1.47)
Standardized/ adjusted for age, sex and education	Any dementia –	11.1%	7.8%	11.8%
	standardized prevalence (%)	(9.7-12.5%)	(5.0-10.6%)	(8.6-15.1%)
	Adjusted prevalence ratio	1 (ref)	0.73 (0.50-1.06)	1.04 (0.79-1.38)
Standardized/ adjusted for age, sex, education and APOE genotype	Any dementia -	11.4%	8.3%	9.7%
	standardized prevalence (%)	(10.0-12.8%)	(5.4-11.2%)	(7.3-12.1%)
	Adjusted prevalence ratio	1 (ref)	0.74 (0.50-1.10)	0.92 (0.69-1.23)

Finally, I assessed the joint, independent effects of admixture and ethnic identity upon prevalence of dementia (Table 23). The first model (Model 1) includes the main effects of APOE genotype and individual admixture. The second model estimates the main effects of APOE genotype and ethnic identity. The third model estimates the effects of admixture and ethnic identity, mutually adjusted, also controlling for APOE genotype. The fourth model extends the third model to control also for the effects of age, sex and education. When the effects of admixture and ethnic identity are considered together (3rd and 4th models) higher levels of African ancestry are associated with a higher prevalence of dementia (PR 4.62, 95% CI 1.48-14.5), whereas 'black' (PR 0.50, 95% CI 0.25-1.00) and 'mixed' (PR 0.54, 95% CI 0.30-0.96) ethnic identity is associated with a lower prevalence of dementia than 'white'. These effects are statistically significant in model 3, but attenuate slightly, and are no longer statistically significant having adjusted, in model 4, for the effects of age, sex and education.

Table 23 The independent effects of admixture and Ethnic identity upon dementia prevalence (weighted analysis)

	Model 1	Model 2	Model 3	Model 4
APOE genotype				
One or more e4 allele	2.21 (1.58-3.09)	2.19 (1.54-3.10)	2.13 (1.50-3.02)	2.45 (1.77-3.40)
Admixture				
100% African versus 100% European admixture	1.53 (0.80-2.91)	-	4.62 (1.48-14.5)	2.55 (0.75-8.61)
Ethnic identity				
‘White’	-	1 (ref)	1 (ref)	1 (ref)
‘Mixed’	-	0.79 (0.47-1.33)	0.54 (0.30-0.96)	0.60 (0.34-1.09)
‘Black’	-	1.02 (0.68-1.51)	0.50 (0.25-1.00)	0.47 (0.22-1.02)
Sociodemographic factors				
Age (years)	-	-	-	1.10 (1.07-1.12)
Male sex	-	-	-	0.84 (0.59-1.21)
Education (per level)	-	-	-	0.76 (0.64-0.90)

Model 1 African admixture and APOE

Model 2 Ethnic identity and APOE

Model 3 African admixture, ethnic identity and APOE

Model 3 African admixture, ethnic identity, APOE, age, sex and education

Figure 8 summarize patterns of association with prevalence and incidence dementia according 10/66 . With regard to the genetic contribution to disease risk, APOE e4 and family history of dementia were associated with both prevalent and incident risk. African admixture and ethno racial identity were not associated with dementia when assessed separately. Non modifiers risk factors as increase age was associated with dementia . Education was a protective factors for dementia prevalence like factors related with early neurodevelopment as skull circumference and leg length. As we previous mention our study weren't suggest that vascular risk factors such as smoking, diabetes, hypertension and lipid profiles play an important role as risk factors of dementia when the exposures are measured in late life very close to probably onset of dementia.

Figure 8. Diagram summarising patterns of associations with prevalence and incident 10/66 dementia.

	Prevalence	Incidence
<u>Genes</u>		
APOE e4	↑	↑
Family history of dementia	↑	↑
Admixture	↔	↔
<u>Environmental</u>		
Sociodemographics		
Age	↑	↑
Sex	↔	↔
Education	↓	↔
Ethnic identity	↔	↔
Anthropometry		
- Skull circumference	↓	↓
- Leg length	↓	↔
Vascular risk factors		
Smoking	↔	↔
Alcohol	↑	↔
Hypertension	↓	↔
Stroke	↑	↑
Diabetes	↔	↔
Cholesterol	↔	↔
Tryglicerides	↔	↔
HDL	↔	↔
Head injury	↔	↔
↑ Risk factor ↓ Protective factor ↔ No association		

CHAPTER 4 DISCUSSION

4.1 Summary of the Results

This study corroborates that dementia is an important and growing health problem for Cuba. The overall prevalence of 10/66 dementia was 10.8% and that of DSM-IV dementia 6.4%. Whatever criterion we use dementia is at least as common in Cuba as in developed countries.

1. According to DSM-IV criteria, after standardisation for age and gender, dementia prevalence in Cuba was similar to that in the European EURODEM meta-analysis and higher than that recorded in other 10/66 Latin American sites. However, an even higher prevalence had been reported in the previous Cuban EDAP survey (SMR 113, 95% CI 108 – 117). The prevalence of 10/66 dementia in Cuba was similar to that reported for other 10/66 Latin American sites in Dominican Republic, Puerto Rico, Peru, and Mexico, and higher than that in Venezuela.

2. Both DSM-IV and 10/66 dementia were associated with older age, less education, a family history of dementia, shorter leg length and smaller skull circumference, associations which are unlikely to be explained by reverse causality.

3. The prevalence of dementia was more than double in APOE carriers compared to that in non-carriers (adjusted PR=2.58, 95%CI 2.06-3.22). This effect was not mediated by

lipid profile or other cardiovascular risk factors, although stroke and diabetes were more prevalent among APOE e4 carriers, and mean total cholesterol levels were higher.

4. There was a particularly large and statistically significant interaction between APOE genotype and VLDL cholesterol subfraction for both 10/66 dementia (PR 2.39, $p=0.01$) and AD (PR 2.16, $p=0.05$) the effect in each case being that VLDL was inversely associated with dementia risk in the absence of an e4 allele (10/66 dementia PR 0.44, 95% CI 0.26-0.74; AD PR 0.85, 95% CI 0.52-1.37), increasing the risk only in the presence of an e4 allele (10/66 PR 1.05; AD PR 1.84), and that the risk effect of APOE e4 was stronger at higher VLDL levels. For the 10/66 dementia outcome, triglyceride was also inversely associated with dementia risk in the absence of an e4 allele (PR 0.80, 95% CI 0.65-0.99), and the risk effect of APOE e4 increased with increasing triglyceride level. There was also a borderline statistically significant interaction, in the same direction, for triglyceride x APOE for the AD outcome ($p=0.06$).

5. Dementia, rather than physical health conditions or depression, was the main contributor to needs for care, to the caregiver needing to give up work to care and to caregiver psychological strain. Those with 10/66 dementia were 17.8 times more likely to need much care, while their caregivers were 13.4 times more likely to have cut back on work to care and 2.1 times more likely to have clinically significant psychological morbidity compared to people without dementia. The severity of behavioural and psychological symptoms was independently associated with each of the three outcomes. The effect of dementia on caregiver psychological morbidity was substantially mediated

through BPS, much more so than the effects on needs for care or on the caregiver cutting back on work to care.

6. The crude annual incidence of DSM-IV dementia was 9.0 /1000 person years while that of the 10/66 dementia was 20.5/1000 person years. Incidence was similar between men and women for DSM-IV dementia, but higher in women than men for 10/66 dementia. Incidence of both outcomes increased exponentially with age.

7. Patterns of association with incident 10/66 dementia were different to those with prevalent dementia. The effect of increasing age was attenuated, particularly when the competing risk of death was accounted for in the analysis. The effect of one or two APOE e4 alleles was also attenuated, and only statistically significant when the competing risk of dementia-free death was accounted for (SHR 1.57, 95% CI 1.05-2.37). The effect of stroke was also attenuated and not apparent when accounting for the competing risk of dementia-free death. The inverse associations with education, skull circumference and hypertension were not apparent with respect to incident 10/66 dementia. Smoking, diabetes, lipid profile, leg length and head injury were not associated with either prevalent or incident 10/66 dementia.

8. The effect of age on incident DSM-IV dementia was less pronounced than that on prevalent DSM-IV dementia, particularly when competing mortality risk was accounted for. There was no association between APOE genotype, or stroke and incident DSM-IV

dementia. There was no protective effect of education, skull circumference or hypertension. Smoking, alcohol use, diabetes, lipid profiles, leg length and head injury were not associated with either prevalent or incident DSM-IV dementia.

9. There was no dose response effect in the association of APOE genotype with incident 10/66 dementia . However, there were only 25 persons in the at risk cohort who were e4/e4, and 255 who had one e4 allele.

10. There was a strong and statistically significant interaction (SHR 0.71, 95% CI 0.53-0.96) between age and APOE genotype in the effect on dementia incidence, which was confined to those in the youngest age group (65–69 years) than among non-carriers. Further analyses confirmed an earlier age of onset for incident dementia among those with one or more APOE e4 alleles, compared with those lacking an e4 allele.

11. There was no evidence for a prevalence bias to account for the discrepancy between associations with prevalent and incident dementia. APOE genotype was not associated with mortality overall, and there was no significant interaction between dementia and APOE genotype in the association with mortality, although the trend was towards a greater mortality risk associated with APOE e4 for those with dementia (interaction term HR 1.34, 95% CI 0.81-2.20).

12. There were no statistically significant interactions between APOE genotype and either stroke, hypertension, smoking, diabetes or lipid profile and the incidence of 10/66 dementia. However, consistent with the cross-sectional analyses there was a trend for the

effect of APOE e4 to increase with the levels of VLDL cholesterol and triglyceride, and for higher levels of these lipids to confer risk for 10/66 dementia in the presence of an APOE e4 allele.

13. Both ethnic group, and African admixture were associated with APOE genotype with e4 frequency being higher in those viewed as 'black' and in those with a higher proportion of African admixture.

14. One or more APOE e4 alleles was associated with dementia in 'white' and 'black' but not 'mixed' groups but neither this, nor the interaction between APOE e4 and African admixture (PR 0.52, 95% CI 0.13-2.08) were statistically significant.

15. Neither ethno-racial identity nor African admixture was associated with dementia prevalence when assessed separately. However, considering their joint effects African versus European admixture was independently associated with a higher prevalence, and 'mixed' or 'black' identity with a lower prevalence of dementia.

4.2 Strengths And Limitations

The major strength of our study is the standardised design and assessment procedures, in a large representative catchment area sample, with high a response rate: 97.6 % in the cross sectional study and 75.8% in the incidence phase.

The whole catchment area sampling strategy enabled us to foster links within the communities studied, improving response and facilitating later follow-up. A weakness of the catchment area sampling strategy is that prevalence and incidence estimates may not be safely generalised beyond these and similar communities, but this is unlikely to lead to bias in estimates of association.

The one phase dementia diagnostic assessment has some advantages over the two phase approach used in most previous dementia cohort studies (Prince, 2003). We were also able to gather detailed information on mental health diagnoses, physical health, risk exposures and care arrangements on all participants, permitting us to study the independent impact of dementia, relative to that of other health conditions, on outcomes relevant to public policy. This has been a neglected research topic. The two and a half hour assessments were well tolerated, as indicated by the high levels of participation in both baseline and follow up interviews.

The diagnosis of dementia was made according to a protocol developed by the 10/66 group using a computerized algorithm The 10/66 dementia algorithm has been carefully

validated in 26 low and middle income country centres (Prince et al., 2003), including Cuba. While sensitivity (94%) and specificity (97% in high education controls and 94% in low education controls) were both excellent against the gold standard of a local clinician's DSM-IV diagnosis, the false positive rate, which varied between 1% and 10% across regions and levels of education can be expected to result in a higher prevalence of 10/66 dementia. Conversely, the DSM-IV criterion, with its stringent requirement for multiple domains of cognitive function to be affected with clear evidence for social and occupational impairment, may be insensitive to mild yet clinically relevant cases (Erkinjuntti et al., 1997). In a recent publication (Prince et al., 2008) we have shown that 10/66 dementia corresponded more closely to Cuban clinical dementia diagnoses than did the more restrictive DSM-IV criterion. Predictive validity of the two diagnoses were determined three years later at the baseline in Chennai, India; 10/66 Dementia cases had experienced twice the mortality of those with cognitive impairment but no dementia (CIND), and the overwhelming majority of those that survived showed clear evidence of progression in cognitive impairment, disability and needs for care (Jotheeswaran AT et al., 2010). The main weakness with respect to ascertainment of the outcome was that dementia subtype diagnoses are not yet available for the incident cases of dementia that we identified in the survey. A computerized algorithm has been developed for the baseline data collection, but this has not yet been published or validated, and requires adaptation before being applied to the incidence wave data. Accordingly, for the prevalence wave data I used the subtype determinations made by the Cuban interviewers (all experienced dementia diagnosticians) having completed the baseline interview. The impact of this on the associations observed is somewhat uncertain. It is likely that associations with APOE genotype would have been

more pronounced for AD subtype than for all dementia subtypes combined, given generally weaker associations observed with vascular and mixed dementia (Verghese P et al., 2011). Studies of environmental risk factors (particularly cardiovascular risk factors and cardiovascular disease) generally show quite similar effect sizes for both AD and dementia; almost by definition, cardiovascular risk factors are likely also to be risk factors for vascular dementia.

Loss to follow-up is the main potential source of bias in cohort studies. If a large proportion of participants are lost to follow-up due to non-response, refusal to participate and withdrawals, and particularly if losses are different between comparison groups, the result may be biased. In our study, a high proportion of the cohort could be traced successfully, and bias from loss to follow-up is likely to be small.

Selection bias may arise from using only people who live at home, that is, our study did not include institutionalised older people, but this is unlikely to affect the prevalence estimate in Cuba as less than 1% of older people live in institutionalised facilities. In the catchment areas studied there was only one institution for older people from all Havana.

Information bias may also have occurred, since the interviewers for the 10/66 surveys were psychiatrists, geriatricians and physicians carrying out clinical work in the same catchment areas where the research project was conducted. Therefore, while the interview was for the most part fully structured, interviewer codings could have been based upon prior knowledge of diagnoses or other previous clinical impressions. However, while we did not collect data systematically, it seemed that only a minority of

those identified with dementia were previously known to services, and very few participants had previously consulted with the clinicians carrying out the interview.

There has been much interest in the potential role of African ancestry in modifying the effect of the APOE genotype and influencing risk for AD and other dementia (Hendrie et al., 2004). The highly admixed character of the Cuban population provided us with an ideal opportunity to study this possibility within, rather than between populations. We believe ours to have been the first study to have addressed this issue directly, through estimation of individual admixture, rather than relying merely on observations of ethnic type. The main weakness of the admixture study was that of the sample size. The high cost of admixture genotyping across 60 SNPs meant that we could only perform this on all dementia cases and a random sample of controls in the cross-sectional prevalence phase of the study. Hence the study may have been underpowered to detect or exclude potentially important APOE genotype by admixture interaction effects..

I am not able to attribute causality from the observed associations between health cardiovascular risk factors and dementia. As lipids levels and other cardiovascular risk factors were determined during the cross-sectional study, in late-life and close in time to the clinical onset of dementia, temporality can not be established and the lack of association might have been explained by reverse causality. For example hypotension and weight loss can be a consequence as a cause of dementia.

4.3 Contextualization with Previous Research

4.3.1 Prevalence of dementia in Cuba

The prevalence of DSM-IV dementia in our study was similar to that previously reported in Europe. In the current sample we demonstrated that the DSM-IV criterion missed many of the CDR mild dementia cases (Prince et al., 2008). The current study adds to the evidence that the prevalence of DSM-IV dementia in Latin American settings is at least as high as that seen in high income countries in Europe and North America. The one caveat is that most Latin American studies published to date, including our own, have sampled from urban rather than rural settings and from countries with relatively low child and adult mortality.

The age-specific prevalence of 10/66 dementia in Cuba was consistently higher than that of DSM-IV dementia, raising the possibility that use of the DSM-IV criterion may underestimate the prevalence of clinically significant dementia. DSM-IV dementia criterion underestimates the true prevalence of dementia in developing countries, because of difficulties in defining and ascertaining decline in intellectual function and occupational impairment. We have attributed this discrepancy to an under-reporting of cognitive decline and social/occupational impairment by relatives: our data suggest that this underestimation might be attributable to cultural effects on informant reports of intellectual decline and social or occupational impairment, specifically a much weaker correlation between objective evidence of memory impairment and informant reports in rural and least developed settings (Llibre Rodriguez et al., 2008b).

According to the DSM-IV criteria, age- and gender-standardised dementia prevalence was higher than that reported for other 10/66 sites in Latin America (Llibre Rodriguez et al., 2008b), although somewhat lower than that reported in a previous EDAP study in Cuba (Nitrini et al., 2009). As the Cuban population is characterised by a relatively high degree of African admixture, and our hypothesis was that high African admixture protects against dementia, how can we explain the high prevalence showed by our data? One plausible explanation is the advanced stage of the epidemiological transition in Cuba, where, along with increased life expectancy, fat-rich diets, smoking and physical inactivity have become more common and reach all sectors of the population. In terms of physical activity, while just 33% of Cubans were sedentary in 1995, this figure increases to 43% in 2001 and 45% in 2010. The overweight trend has increased in the general population aged 15 years and older from 32% in 1995, to 45% in 2010; the prevalence of hypertension in the same age group is also high 30.9% in 2010 (Reed G and Bonet M, 2011).

A particularly high prevalence of vascular risk factors and of chronic non-communicable diseases were found in our study populations in Havana and Matanzas (Llibre J 2011) hypertension 73.0% , diabetes mellitus 24.8% , ischemic heart disease 14.1% and stroke 7.8%. The majority of participants (85%) had more than one cardiovascular risk factor. One fifth of those surveyed were current smokers, and 7.5% were classified as high-risk drinkers before age 65 and 3.6% were still in this category. A cohort effect may have been in operation with respect to Cubans with an African background were born 65 or more years ago, many of whom would have lived in early life and early middle age in

conditions of poverty, with poor access to health services, lower education and occupation attainment as a result of disadvantage and discrimination.

4.3.2 Incidence of dementia in Cuba

We managed to successfully trace and re-interview 1,892 (75.2%) people out of 2,571 older people free of dementia at baseline, and indentified 171 incident cases of dementia with a total of 8,679 person years of follow-up. Incidence rates provide the information to predict future case-loads, and for this reason are crucial in planning health services for people with dementia and their families, particularly initiatives to promote early diagnosis and treatment (Alzheimer's Disease International, 2011). Few incidence studies have been conducted in low and middle income countries, and the current study is the first longitudinal study of dementia to be carried out in Cuba and one of the very first in Latin America. Our study is also the largest yet conducted in a low or middle income country; in Ballabgarh, India nine incident cases were identified with 1,160 person years of follow-up (Chandra et al., 2001); in Cantanduva, Brazil, 50 incident cases and 3,623 person years of follow-up (Nitrini et al., 2004) . In Ibadan, Nigeria (2,459 at risk and 70 incident cases (Hendrie et al., 2001) and Beijing, China (825 at risk and 13 incident cases (Li et al., 1991) person years of follow-up were not clearly specified.

The crude annual incidence rate for 10/66 dementia was 20.5 /1000 person year, very similar to that found in the Canadian Health and Aging Study (The Canadian Study of Health and Aging Working Group, 2000), and slightly higher than that reported in the

MRC Cognitive Function and Ageing Study (MRC CFAS) in England (Matthews F et al., 2005). Nevertheless according to DSM-IV criteria our estimates were 9.0/ 1000 person year, roughly the half the rates observed in the Canadian and English studies, both of which used DSM-IV criteria. However, to estimate the incidence of DSM-IV dementia, we excluded all those with ‘any dementia’, that is either DSM-IV dementia or 10/66 dementia from the baseline ‘at risk’ cohort. This decision is justifiable on the grounds that there is considerable accumulated evidence for the validity of the 10/66 dementia diagnostic criterion. However, for the purposes of comparison with other studies, it might be appropriate to consider meeting criteria for 10/66 dementia, but not for DSM-IV dementia as still ‘at risk’ for the latter outcome. In the Cuban sample the annual incidence rate for DSM-IV dementia among those in this group was 154.6 per 1000 person years (95% CI 103.9-221.8). After including this group in the ‘at risk’ cohort, the overall incidence rate for DSM-IV dementia increased from 9.0 to 12.0 per 1000 person years (95% CI 9.8-14.4)

4.3.3 Risk factors for dementia

When analyzing the prevalence phase data, we limited ourselves initially mainly to the study of associations with those potential risk factors for dementia that might, arguably, be less affected by reverse causality and information bias; educational level, and early developmental factors – skull circumference, leg length and handedness (Llibre Rodriguez et al., 2008a). The main cross-sectional correlates of dementia (older age, lower education and family history of dementia) were generally similar to those

previously and widely reported. We confirm previous reports of shorter leg length (Kim et al., 2003, Mak et al., 2006), and smaller skull circumferences (Schofield et al., 1997, Mortimer et al., 2003) among those with dementia. Interestingly both of these exposures were inversely linearly associated with age suggesting the presence of cohort effects; older people, from earlier birth cohorts, having poorer nutrition and hence having developed less successfully in early life. Adjusting for age, which diminishes the strength of both associations, may be inappropriate. We did not replicate previous reports of associations between handedness (Seltzer et al., 1984, de Leon et al., 1986, Li et al., 1992, Raiha et al., 1998) and dementia. We also found no evidence to support associations with a past history of head injury (Mortimer et al., 1991, Jellinger, 2004, Devanand et al., 1996) or a past history of depression (Jorm et al., 1991, Devanand et al., 1996) and dementia. Data on these exposures was collected from participants, or from their relatives if they were considered to give more reliable information. While recall bias is often thought to lead to an overestimation of such associations because of ‘effort after meaning’, lack of an association might conceivably be explained by random or systematic misclassification because of poor recall by those with dementia or their relatives.

For the incidence phase of the study, I broadened the scope of the analysis of potential risk factors, to include, particularly cardiovascular risk factors (smoking, hazardous alcohol use, hypertension, diabetes and lipid profile. Since all of these potential risk factors for dementia are also likely to be risk factors for dementia-free death, I conducted two sets of Cox’s proportional hazards regression analyses, one with, and one without taking into account this competing risk. As a methodological exercise, I also

estimated the cross-sectional associations between these risk factors and prevalent dementia, in an attempt to understand better the potential impact of information bias and reverse causality on the estimation of these effects using cross-sectional data. In general, I found no evidence to reject the null hypothesis of no association between cardiovascular risk factors and incident dementia. Stroke, alone, was significantly associated with the onset of 10/66 but not DSM-IV dementia; however, this association attenuated and was no longer statistically significant after accounting for the competing risk of dementia-free death. Smoking, diabetes and lipid profile were associated neither with prevalent nor incident dementia. Hypertension was inversely associated with prevalent dementia, but appeared to have no effect on incident dementia. A history of hazardous alcohol use before the age of 65 was associated cross-sectionally with 10/66 but not DSM-IV dementia. There were strong non-statistically significant trends towards an association with both incident 10/66 and DSM-IV dementia. This was a low frequency exposure, and the study was probably underpowered to detect a true association. The inverse associations with education seen in the cross-sectional analyses were not supported for incident dementia in Cuba; the effect sizes being attenuated and no longer statistically significant. The same pattern was seen for the cross-sectional inverse associations with leg length and skull circumference, with non-significant trends towards positive associations with incident dementia.

The absence of observed associations between cardiovascular risk factors and incident dementia may not be surprising given that exposures were measured in late-life, and the relatively short follow-up period (a median of 4.1 years). A recent meta-analysis of cohort studies of the effect of hypertension on incident AD found a trend towards an

inverse association with late-life hypertension but a suggestion of a positive association with mid-life hypertension (Power MC et al., 2011). This pattern was clearly demonstrated in the Goteborg study, where those who went on to develop dementia in late-life had relatively elevated blood pressure levels up to 15 years previously, which then declined to levels below those of the dementia-free participants by the time of dementia onset (Skoog et al., 1996).

A similar process may explain the lack of associations observed between lipid profile (total cholesterol and cholesterol subfractions, and triglyceride) and dementia in my study. A recent meta-analysis identified 18 prospective studies of the association between total cholesterol and the incidence of either dementia or cognitive decline. Follow-up periods ranged between 3 and 29 years (Anstey KJ et al., 2008). There was no evidence for any association between late-life cholesterol and either outcome, but there was robust and consistent evidence for associations between mid-life hypercholesterolaemia and incident AD, incident dementia and cognitive impairment. The association observed in some long-term prospective studies between decline in cholesterol and incident cognitive impairment (Solomon A et al., 2007) and dementia (Stewart R et al., 2007, Mielke M.M et al., 2010) suggests that cholesterol begins to decline years before the onset of dementia, possibly as a result of ongoing AD pathology (i.e. reverse causality (**see also section 1.4.1.5 for further details**)). Another possible explanation for the failure to detect any association between cholesterol, triglyceride and dementia, may be that the effect of these lipids is significantly modified by APOE genotype. We examined this possibility using cross-sectional data – these analyses are discussed later in this section.

The absence of associations with reported smoking behaviour is perhaps more surprising since risk associations have previously been noted in short latency (Ott et al., 1998b, Juan et al., 2004, Luchsinger et al., 2005) as well as long latency studies (Tyas et al., 2003, Whitmer et al., 2005). The 10/66 Dementia Research Group has also reported an increased risk of AD as well as all forms of dementia, from prevalence data, when the smoking exposure was pack years consumption before the age of 50 (Ferri et al.,2011). Earlier findings of an inverse association with smoking from case-control studies using prevalent cases and cross-sectional studies have been attributed to prevalence/ incidence bias (Neyman's bias) due to a failure to take account of the effect of the risk exposure on mortality (Hill et al., 2003). However, it should be noted that there are other examples in the literature of a failure to replicate findings of an association between smoking and incident dementia (Yip et al., 2006).

Hazardous alcohol user before the age of 65 was associated with dementia in the cross sectional study (PR= 1.69; 95% CI 1.18-2.41), but not in the longitudinal phase. There are controversial findings in the literature, which some studies advocating its protective effects (Letenneur L et al., 2004, Peters R et al., 2008) and others its potential risk effects (Anttila et al., 2004).

There have been reports from cohort studies of short latency associations between diabetes and the onset of dementia. For example in the Rotterdam study, with an average follow-up of only 2.1 years diabetes was found to almost double the risk of both dementia (RR 1.9, 95% CI 1.3-2.8) and AD (RR 1.9, 95% CI 1.2-3.1). However, more

recent meta-analyses suggest much more modest risk associations; pooled RRs of 1.47 (95% CI 1.25–1.73) (Lu FP et al., 2009) and 1.54 (95% CI 1.33–1.79) (Profenno LA et al., 2010); with the majority of individual studies not showing statistical significance. It is therefore possible that my study was underpowered to detect a relatively small true increase in risk for incident dementia, despite the relatively high prevalence of diabetes in the the ‘at risk’ cohort. There is also a suggestion from at least one study that the effect of diabetes on dementia risk may be extensively modified by APOE genotype, indeed only apparent among those with low dementia risk, lacking any APOE e4 alleles (Akomolafe A et al., 2006). I also examined this possibility (see later section of discussion).

Educational level was inversely associated with the prevalence of dementia (PR 0.80; CI 95% 0.72–0.89). Nevertheless, the inverse associations with education were not apparent with respect to incident 10/66 dementia HR 0.93 (0.81–1.08). Longitudinal studies have shown that lower educational attainment is associated with an increased risk of dementia in late life (Letenneur L et al., 1999, Stern et al., 1994, Evans et al., 2003); although this finding has not been replicated in all studies (Cobb JL et al., 1995). Education in early life is related to higher socioeconomic status, nutrition, and IQ, and influences risk factors in later life such as occupation, physical health, and health habits all of which may protect against the development of brain disease and consequent dementia, particularly vascular brain disease (Del Ser T et al., 1999). Finally education increases cognitive reserve by offering long-term potentiation-induced neuroprotection (Addae JI et al., 2003).

I did not analyze the effect of occupational attainment on 10/66 Dementia incidence. A recent review identified nine out of 12 studies in high income countries demonstrating a statistically significant protective effect, with a pooled OR for incident dementia for those with high compared with low occupational attainment of 0.56 (95% CI 0.49–0.65) (Valenzuela MJ and Sachdev P, 2006).

4.3.4 Genetic epidemiology – analyses of the main effect of APOE genotype on dementia risk, and its role as an effect modifier

I found a strong association between APOE genotype and the prevalence of both 10/66 and DSM-IV dementia, and the prevalence of AD, with effect sizes very similar to those reported in other settings (Farrer et al., 1997, Bertram et al., 2007). In our Cuban sample the risk of dementia and AD conferred by APOE e4 was also similar to that association reported in Maracaibo, Venezuela (Molero A et al., 2001). There have been two reports of studies of the association of APOE genotype with dementia among Hispanics from the Caribbean region living in the USA. Our findings are consistent with the report of a strong association among Cuban Americans living in Miami (Sevush S. et al., 2000), but did not concur with the absence of an association reported among Caribbean Hispanics living in north Manhattan (Tang et al., 1998). As others have found (Prince M, 2000) the effect did not appear to be mediated by cardiovascular risk or cardiovascular disease, although I did find higher levels of total cholesterol, and a higher prevalence of stroke and diabetes among APOE e4 carriers compared with non-carriers.

However, the association between APOE genotype and incident dementia was, in comparison, much attenuated. There was only borderline statistical significance for the association with incident 10/66 dementia; HR 1.48 (95% CI 0.98-2.24) without and 1.57 (95% 1.05-2.37) with accounting for competing risk of dementia-free death. For incident DSM-IV dementia no association was observed; HR 1.04 (95% CI 0.53-2.03) without and 1.09 (95% CI 0.56 -2.11) with accounting for competing risk of dementia-free death.

The reason for this much reduced strength of association with incident as opposed to prevalent dementia is not immediately clear, and may be complex. One possible explanation, that APOE e4 prolongs survival with dementia rather than increasing its incidence seems unlikely given the weak effect of APOE genotype on overall survival, and the absence of an interaction between dementia status and APOE genotype as risk factors for mortality (see page 141). A likelier explanation is suggested by the strong interaction observed between age and APOE genotype in risk for onset of 10/66 dementia, the increased risk conferred by the APOE e4 allele seeming to be confined to those in the younger-old age groups (**see also section 4.4.3**). A further analysis revealed that there was a very strong effect of APOE genotype on age of onset with those having an APOE e4 allele having a mean age of onset 4.6 years earlier than those lacking an APOE e4 allele who went on to develop dementia (see figure 6, p 139). Both the concentration of risk among the younger-old, and the younger age of onset among APOE e4 carriers were noted 15 years ago in clinical samples by members of the NIMH genetics initiative (Blacker D et al., 1997). A similar phenomenon was illustrated in the US Cache County study, where APOE genotype was found to influence age of onset, but

not lifetime (up to 100 years) cumulative risk of dementia which was similar (72%) for those with and without APOE e4 alleles (Khachaturian AS et al., 2004). It may be that our prevalence study had already captured much of the (earlier) cumulative incidence in those who had their risk for early incidence raised through carriage of one or more APOE e4 alleles. When these individuals were eliminated from the ‘at risk’ group for the cohort study, it would therefore be predicted that the association, in the remaining cohort, with incident dementia, would be less prominent. Set against this, while there have been very few previous population-based studies of the effect of APOE genotype on the incidence of dementia, findings from the UK MRC-CFAS study do indicate a robust and sizeable increased relative risk (Yip AG et al., 2002). Of note, in that study, the size of the effect of APOE genotype increased with longer-term follow-up, up to 10 years from baseline; at that point, relative to those with APOE e3/e3 genotype, those with e3/e4 had a RR of 2.3 (95% CI 1.5–3.6) and those with e4/e4 a RR of 5.0 (95% CI 1.9–13.0) (Keage H et al., 2010).

4.3.5 Interaction between genetic admixture, ethnic identity, APOE genotype and dementia prevalence in an admixed Cuban sample; a cross-sectional population survey and nested case-control.

In the catchment area samples of older Cubans in Havana and Matanzas cities, ‘white’, ‘mixed’ and ‘black’ ethno-racial groups were all substantially admixed, with varying proportions of African and European ancestry. There was a strong and statistically significant association between both ethnic identity and admixture, and the APOE genotype, the e4 allele being over-represented in ‘mixed’ and ‘black’ ethnic groups and in those with greater African admixture. The association between APOE genotype was evident among those identified by interviewers as ‘black’ as well as those identified as ‘white’, but not in those identified as ‘mixed’. There was a non-significant trend for the association between APOE genotype and dementia to be weaker in those with greater degrees of African admixture. These findings are in contrast to those from the Ibadan study in Nigeria, where, in the West African context, there was no association between APOE genotype and Alzheimer’s disease (Hendrie et al., 1995a, Gureje et al., 2006, Osuntokun et al., 1995). However, associations were observed among African Americans in the Indianapolis, USA arm of the same US-Nigeria study (Hendrie et al., 1995a, Gureje et al., 2006, Osuntokun et al., 1995). It should be noted, again, as a potential limitation, that our findings relate to the outcome of dementia, rather than AD as in the US-Nigeria study.

Controlling for ethnic identity or admixture did not affect the association between APOE genotype and dementia, suggesting an absence of confounding by population stratification. After controlling for compositional differences in APOE genotype (the risk conferring e4 allele being more common in ‘mixed’ and ‘black’ ethno-racial identity groups), there was a non-significant trend towards lower dementia prevalence in those

‘non-white’ groups. A similar non-significant trend was apparent for admixture. However, when the joint independent effects of ethno-racial identity and admixture were assessed in a single model, mutual confounding was evident. In each ethnic identity, increased African ancestry greatly increased the risk of dementia. At every level of African ancestry, those with ‘mixed’ and ‘black’ ethno-racial identities had a lower risk of dementia. Our findings on the effect of admixture on dementia prevalence are inconsistent with suggestions from a recently published Brazilian brain bank study, in which higher levels of African admixture were associated with lesser degrees of Alzheimer-related neuropathology (Schlesinger D et al., 2011). However, while this latter finding is supportive of the hypotheses that genes linked to African ancestry might protect against AD, one cannot exclude the possibility that it may have been accounted for by selection biases for inclusion into the brain bank (with those with more African ancestry and AD being less likely to be included).

We have therefore established a link between admixture and APOE genotype, with a higher frequency of the risk-conferring e4 allele in those with greater degrees of African admixture. This tendency has been noted between populations with and without African ancestry (Farrer LA, 1997), but never before confirmed with respect to individuals with differing proportions of individual admixture. All things being equal, in a population with significant African admixture, this would be expected to result in a greater incidence and prevalence of dementia. However, in our sample this was offset by a large attenuation of the effect of APOE e4 in those with more African ancestry. This interaction was not statistically significant, and larger samples will be required to measure this with more precision and exclude type II error. Also, there was no

significant graded effect modification by ethnic identity in the larger sample, with the attenuation of effect being confined to those in the 'mixed' group.

Another balancing effect on overall prevalence may be in operation given that the effects of 'mixed' or 'black' ethno-racial identity on the one hand, and African genetic admixture on the other seem to be operating in opposing directions in influencing dementia risk. Genetic admixture, externally observable physical characteristics including skin colour, and self-reported ethnicity are related to each other, but in complex ways (Parra et al., 2004, Airhihenbuwa et al., 2000). These are therefore related yet by no means collinear constructs, and mutual confounding is feasible. The new respectability of observer assessments of 'ethno-race' in epidemiological research arise precisely from their ability to identify the externally observable physical characteristics that are hypothesised to lead to social, economic and health disadvantage. Much research in the US has focussed upon black ethnic identity as a socially determined, contextually bound construct, linked to disadvantage and discrimination, and mediating health disadvantages. Thus, in the 1990s darker skin colour among African-Americans was found to be inversely associated with income, education and occupational status, and to be a stronger predictor of adult occupational status than was parental socioeconomic position (Jones, 2001). More recently, darker skin colour has been shown to be independently associated with experiences of racism (Keith and Herring, 1991). Protective income gradients in hypertension are evident for light-skinned but not dark-skinned African-Americans, an effect hypothesised to be explained by psychosocial stressors linked to skin colour, including racism (Klonoff and Landrine, 2000). Of relevance to our finding of an apparent protective effect of non-white ethno-racial

identity on dementia risk, some benefits of such self-identification have been reported; for example factors reflecting participation in and belonging to African-American culture were associated with a range of positive health behaviours (Sweet et al., 2007).

One of the weaknesses in the current study is that we did not adequately separate out self-perceptions from observer ratings of ethnic identity. A related issue is that ascertainment of race using interviewer's perception might affect the estimate of the prevalence of dementia in different ethnic groups and introduce bias in the associations reported. However, our estimates of African and European ancestry by SNP admixture analysis correlate more or less as one would have predicted with the interviewer's perception of race (black, mixed or white) (ANOVA for linear association $p < 0.001$). This provides some concurrent validation for both the SNP estimating procedure and the interviewer perception. The main conclusion to be drawn is that a proper understanding of the role of genetic admixture in determining disease risk may require measurement of, and control for each of these and other related socio-cultural factors, including socioeconomic position and acculturation (Klimentidis et al., 2009, Jones, 2001) . Although strongly correlated, the effects of admixture and ethno-racial identity on health outcomes can and should be distinguished when assessing genetic and environmental contributions.

4.3.6 Effect modification of the effect of cardiovascular risk factors on dementia risk, by APOE Genotype

I did not find any significant difference in effect of cardiovascular risk factors on incident dementia risk by APOE genotype (p 136). Neither was there any consistent pattern or trend in the interaction effects observed across cardiovascular risk factors.

Stroke and APOE e4 are independent risk factors for dementia. Synergetic effects between cerebrovascular disease and APOE e4 on the risk of cognitive decline were reported in a European community-based study of 353 men (Gerrish et al., 2012). I did not find an interaction of APOE and stroke for the incidence of 10/66 dementia. The same results were found in the Canadian Study of Health and Aging, where the joint presence of stroke and APOE e4 was associated with a greater risk of dementia compared with absence of these two factors, although the effect of stroke on dementia did not seem to be modified by APOE e4 (Keage et al., 2012). A probable explanation seems to be that stroke and APOE e4 may lead to dementia via independent mechanisms.

Our study provided some evidence to support effect modification by APOE genotype of the association between smoking and dementia (SHR in APOE 4 carriers = 1.97 versus SHR in APOE 4 non carriers = 0.89), but this interaction was not statistically significant. The association between smoking, dementia, and APOE genotype is controversial. The Rotterdam Study (Ott et al., 1998b), reported an increased risk of dementia and AD associated with smoking in those without the APOE e4 allele. However, due to the disproportional mortality rates between smokers and nonsmokers who are APOE e4

carriers, the question remains whether there are additional factors in the causal chain possibly related to vascular disease.

Diabetes mellitus was not an independent risk factor for dementia in the overall Cuban Study sample. We also did not find effect modification by APOE genotype. The Kungsholmen project (Hampton et al., 2011) reported no interaction between DM and the APOE ϵ 4 genotype, while the Honolulu-Asia Aging study (Peila R et al., 2002) observed a higher RR among diabetic patients with an APOE ϵ 4 genotype.

In a meta-analysis conducted by Anstey et al (Anstey KJ et al., 2008), only two of seven studies reporting data on the interaction between total cholesterol and APOE ϵ 4 allele in the association with dementia had significant effects. In a population-based study of elderly Yoruba living in Ibadan, Nigeria, Hall et al found (Hall KS, 2006) that increasing levels of cholesterol and LDL were associated with increased risk of AD in individuals without the APOE ϵ 4 allele, but not in those with APOE ϵ 4. They also reported a significant interaction between triglycerides, APOE4, and AD risk, but in the opposite direction; increased levels of triglycerides were not associated with an increase in the risk of AD for individuals without the ϵ 4 allele.

I also found stronger effects of triglyceride and VLDL cholesterol on dementia risk among those with an APOE ϵ 4 allele. These interactions were statistically significant in the cross-sectional analysis, with a non-significant trend in the same direction in the incidence analysis. VLDL transports endogenous triglycerides, phospholipids, cholesterol and cholesteryl esters. It functions as the body's internal transport mechanism

for lipids. VLDL levels have been correlated with accelerated rates of atherosclerosis and are elevated in a number of diseases and metabolic states.

4.4 Conclusion

The prevalence and incidence of dementia in the older Cuban population is relatively high, and the rates increase with age. These findings underscore the need to improve our understanding of risk factors associated with dementia in specific populations, as well as the need for public health programs for both patients and caregivers in a population that is currently demographically ageing and well advanced in the epidemiological transition.

Regarding dependence I demonstrated that dementia is one of the most important contributors to needs for care, to the caregiver needing to give up work to care and to caregiver psychological strain.

In this community-based population longitudinal study, some well-known risk factors for dementia, are confirmed but not others. Older age, a family history of dementia and APOE e4 genotype were independent risk factors for incident 10/66 dementia. Smoking, diabetes, lipid profile, leg length and head injury were not associated with either prevalent or incident 10/66 dementia. New cohort studies are needed to study the effect of cardiocascular risk factors from mid- to late-life.

In our Cuban sample the risk of dementia and AD conferred by APOE e4 was 2.5 times higher than in APOE e4 non carrier after controlling the effect of age, gender and education and family history, which tended to increased slightly after adjusting for serum total cholesterol, other risk factors and vascular disease. The study shows that the

relationship between APOE e4 and incident dementia is stronger in younger old persons than in older old persons and that this change must be taken into account in models of dementia .

We found a significant interaction between triglycerides and dementia, but not for cholesterol. For individuals with an APOE e4 allele, increasing level of triglycerides and VLDL were associated with increased risk of dementia. APOE genotype needs to be considered when assessing the relationship between lipid levels and dementia risk in population studies.

APOE genotype is strongly associated with ancestry. Larger studies are needed to confirm whether the concentration of the high-risk allele in those with African ancestry is offset by an attenuation of its effect. Counter to our hypothesis, African admixture may be associated with higher risk of dementia, once the effect of discernable ethnic group status is controlled for. Although strongly correlated, effects of admixture and ethnic identity should be distinguished when assessing genetic and environmental contributions to disease risk in mixed ancestry populations.

4.5 Implications

4.5.1 Implications for Clinical Practice

Epidemiological studies into dementia can generate awareness, inform policy, and encourage service development. Results presented in this thesis indicate that dementia is an increasing health and social problem in countries like Cuba with an important burden for families, services and society.

Health systems in LMIC tend to prioritise delivery of care for communicable diseases and services related to maternal and child health. There is also the tendency to focus on the development of treatments for chronic diseases while falling to adopt a broader perspective integrating the delivery of care for all chronic diseases within primary and secondary care (Reddy K, 2011).

In Cuba an integrated approach to chronic conditions began in 1999 and had been completed as a strategic plan through to year 2000 (Tang M.X et al., 1996, Reed G, 2008) when programs addressing to national prevention and management of chronic diseases including hypertension, diabetes, atherosclerosis, stroke and coronary heart disease were implemented by the Minister of Public Health. As part of this strategy, strengthened primary health care through the adoption of the family doctor-and-nurse model, locating health professionals at the neighborhood level, and training them to promote health, were considered to be important issues for the management of risk factors and NCDs. The point was to prioritize attention to NCDs at the same level as maternal-child health and infectious diseases. Nevertheless, more concerted attention is

already being paid to these diseases and their risk factors through generating better media messages, enforcing legislation, using leverages such as pricing, and above all, pursuing coordinated multisectoral initiatives.

With the rapid ageing process and the increase in numbers of people with dementia clinicians need to be aware and well trained for early detection, treatment and support for the people with dementia and their families. Doctors and in particular those from the primary level should be able to make an early diagnosis of dementia, prevent and manage comorbidities and optimise physical health, cognition, activity and well-being of their patients. The detection and treatment of behavioural and psychological symptoms enhances the good quality of life for patients and their caregiver, and at the same time, may reduce the proportions of those who need nursing homes. They will also need to be prepared to provide information and long-term support to carers.

Packages of care (combinations of treatments) for dementia have been proposed to achieve optimal outcomes in improving and managing the condition (Prince et al., 2009). The principal goals in managing dementia in health care are: detection and early diagnosis through dissemination of information about the condition; optimization of physical health, cognition activity, and wellbeing through regular physical assessments and cognitive stimulation intervention; detection and treatment of BPSD through dissemination of information and pharmacological treatments; and the provision of information and long – term support for carers (Prince et al., 2009).

According to the Alzheimer's disease International the minimum actions recommended for dementia care are (Prince M et al., 2007):

1. Provide treatment in primary care
2. Make appropriate treatment available
3. Give care in the community
4. Educate the public about the condition
5. Involve communities, families and consumers in advocating for dementia
6. Established national policies, programmes and legislations for dementia
7. Develop human resources through training of health workers to care for dementia patients
8. Create links with other sectors like non governmental organizations
9. Monitor community health
10. Support more research

As a developing country, Cuba has limited economic resources and cost-effective responses could be adapted and expanded to improve dementia care. This strategy could be centred in the enormous human resources to allow the implementation of the National Strategy. LMIC as India has succesfull implemented national strategies on dementia (Alzheimer's and Related Disorders Society of India, 2010).

I summarise the main features of the proposed packages of care for dementia in Cuba:

1. Raising awareness about the importance of early diagnosis and intervention on dementia, providing information, education and families suport .
2. Strengthening the health system in particularly training of the health and social care workforce at primary level .

3. More research should be commissioned towards biomedical research, risk factors, quality of life, and health services.
4. All primary care services should have basic competency in the assessment of cognitive impairment, making and imparting a provisional dementia diagnosis, and initial management of dementia and refer to the indicated specialist.
5. Increase the availability of specialised health workers in the dementia field, such as geriatrician, neurologist, psychiatrists, nurses, psychologist and social workers at the primary health level, to confirm early stage dementia diagnoses and formulate care management plans.
6. The availability of effective drug and non-drug interventions for people with dementia and their carers should be publicised to health and social care professionals through initial training and ongoing professional development, and to the public through population health promotion, and health and social care facilities.

Better understanding of genetic risk factors for dementia, and gene-environment interactions, may help in the future to identify individuals at higher risk to develop dementia, and to provide targeted advice on behavioural and lifestyle risk factor management. In the Cuban context, knowledge of individual admixture, and the genes linked to ancestry that might play a role in dementia risk, could have a part to play in future health care. However, our findings, while interesting, do not have any immediate clinical applications. More research is required, with larger study samples, to address this issue in more detail.

4.5.2. Implications for Health Services Programme

I believe that the prevalence and incidence estimates contained in this thesis constitute the best currently available basis for Cuban policymaking, planning and allocation of health and welfare resources regarding dementia.

As trend for life expectancy is to increase, numbers of people with dementia will continue to grow, particularly among the oldest old and more and more among whom comorbidity is a particular issue. An urgent political priority will be formulation of policies and plans to scale up provision and finance their long term care needs, including support for family carers.

There are three experiences to provide care and promote health at the primary levels in Cuba, which at a modest cost , have provided useful support for older care. The Senior Centers (Casas de Abuelos), of which there are 233 in the country and 25 in Havana supported by the health system, offer caregiving, meals, and social and recreational activities during the day for older adults (Ministry of Public Health, 2009). This is especially important for those who either live alone or are home alone while other family members are at work or school. In another sphere, the Older Adult University, an outgrowth of the University of Havana, now has over 600 classrooms in local institutions and centers across the country—many in the capital— bringing continuing

education opportunities to the community level. Inter-generational concerns, living an active life at an older age, and other issues particularly relevant to this age group are central to the curriculum. The third institution are Senior Circles (Círculos de Abuelos), supported by family doctors and polyclinics, offer a good example of how a small investment can impact many peoples' lives—in this case, offering opportunities for regular exercise promoting physical and mental health, plus essential social contact. By 2005, over 700,000 older adults across Cuba were participating in these circles (Malagón Y et al., 2007).

4.5.3. Implications for promotion and prevention

The high prevalence of dementia in the elderly population means that intervention is likely to have a high impact and be cost effective. A comprehensive effort to address the chronic disease epidemic and cardiovascular risk factors as risk factors for dementia will be most effective when clinical prevention is combined with population-level prevention policies.

While my study has not provided additional evidence to support the role of cardiovascular risk factors and cardiovascular disease as aetiologic factors for dementia, the evidence from other studies is strong, particularly those that assessed the effects of mid-life as opposed to later-life levels of exposure. Primary disease prevention measures are therefore important and relevant.

Primary prevention should focus upon targets suggested by current evidence; improving access to education, detection and control of hypertension, hyperlipidaemia, diabetes, obesity and metabolic syndrome factors, and physical inactivity, should in principle have an important impact on the future prevalence and incidence of dementia worldwide. If all of the risk factors were eliminated, then a total of up to 50.7% of all cases of AD worldwide might be prevented (Barnes and Yaffe K, 2011). The most promising strategies in terms of yield of cases prevented would come about through the elimination of physical inactivity (12.7% of AD cases prevented), smoking (13.9%) and low education (19.1%) (Solomon A. et al., 2007).

World Health Organisation (WHO) estimates that up to 80 percent of cardiovascular disease, stroke, and type 2 diabetes could be prevented by eliminating shared risk factors such as tobacco use, unhealthy diet, physical inactivity, and the harmful use of alcohol (World Health Organization, 2006) . Continuing to strengthen primary health care would be the most promising strategy for management of risk factors and disease. At population level, cost-effective measures include the implementation of tobacco-free policies, tobacco taxation, comprehensive bans on advertising of tobacco products, food labeling, salt reduction through voluntary agreements with the food industry, educational efforts, and combination drug therapy for those at high risk of cardiovascular disease.

4.5.4 Implications for research

Cross sectional studies such as the 10/66 surveys provide local estimates on prevalence of diseases, inform the community, policymakers and health services about the contribution of these conditions for future prioritisation, and promote understanding about the societal cost of dementia.

However, there is a continuing need for such studies, to investigate changes over time in risk factors, chronic disease prevalence and incidence, functioning, disability and dependence. Longitudinal studies are one of the methods that can be used to measure such trends. Panel surveys with repeated representative prevalence phase samples can also be adopted to achieve the same goal without the logistic and feasibility issues that may arise from a longitudinal design. Data from repeated waves will be able to provide us with details on differences in these trends, their possible causal explanations, and the extent to which these trends are attributable to increased surveillance and earlier diagnosis, increases survival with disease, or to cohort differences in the underlying disease-disability processes (Jagguer et al. 2007). Effectiveness of implemented interventions can also be assessed through such studies and its results may influence planning for future health programmes tailored to the population under study.

The 10/66 cross-sectional study in Cuba was conducted from 2003 to 2006. I have now received further funding from the Cuban government to repeat the cross-sectional surveys in the same catchment area sites approximately 10 years on. This will allow me

and my research group to provide Cuban policymakers with information about the course of the chronic disease epidemic among older people, and the specific impact upon dementia prevalence, disability, dependence and care.

The research conducted to date has highlighted the burden of dementia in Cuba for individuals and their families. It is important that more research to understand and treat the problem locally is developed. The World Health Organization has developed evidence based guidelines for the management of dementia (m GAP) (World Health Organization, 2008b) to be used in primary care, and it is important to test new approaches for the management of dementia in the Cuban primary health that can be cost effective.

We have found some evidence that that APOE genotype modifies the association between both triglycerides and the VLDL cholesterol subfraction and dementia. However we measured cholesterol and lipid profile in late life. Ideally, future research should be conducted using longer term follow-up between middle age and late life. Any such study would be costly and requires a long-term funding commitment. However, the benefits of such long-term cohort research extend far beyond a better understanding of the aetiology of dementia.

We clearly found a linear trend of increased APOE e4 alleles with dementia and with increased African ancestry, but I failed to demonstrate that the association between APOE e4 alleles and dementia was significantly modified by African ancestry. However, we

have conducted this analysis in a small subsample and hopefully will be able to carry on this analysis with the whole sample as material has been stored. Although are results are not conclusive it highlights the trend and the importance to further research in this area to confirm whether the concentration of the high-risk allele in those with African ancestry is offset by an attenuation of its effect.

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ANNEXES

ANNEX 1

Llibre Rodriguez JJ, Ferri CP, Acosta D, Guerra M, Huang Y, Jacob KS, Krishnamoorthy ES, Salas A, Sosa AL, Acosta I, Dewey ME, Gaona C, Jotheeswaran AT, Li S, Rodriguez D, Rodriguez G, Kumar PS, Valhuerdi A, Prince M; 10/66 Dementia Research Group. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. *Lancet*. 2008 , 9;372(9637):464-74.

ANNEX 2

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ANNEX 3

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